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THE VALUE OF MATERNAL MORTALITY SURVEYS*

Presidential Address

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AS OBSTETRICIANS and gynecologists from the central section of the United States we are assembled here to discuss the problems arising in the practice of our special field of medicine. A group such as the Central Association must exert significant force in developing a highly effective practice. Many of you will recall the ideals and practical advantages which led to the founding of this association, dedicated to raising the level of practice in obstetrics and gynecology.

I deeply appreciate the privilege of being able to offer at this time some suggestions on the conduct of maternal mortality studies. My close association with the Minnesota surveys has prompted the subject matter of this presentation.

Through the recent education program of the American Medical Association we have all been convinced that there will be less to fear from innovations by politicians like Oscar Ewing if we make an honest attempt to put our house in order. Since the medical profession has the requisite knowledge and information, *it* must be the group to develop the means of producing the desired results. To any mature thinker, our objection to socialization is based on the fact that it produces, inevitably, a dead level of mediocre performance.

Because we, as obstetricians, are directly responsible for the entire picture of childbirth, it becomes vitally important for us to examine and evaluate all procedures. Such a study will reveal our effectiveness in the practice of obstetrics, and will point up pertinent needs in attaining a still higher level of accomplishment.

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Throughout the civilized world, wherever vital statistics are kept, the mortality rate associated with pregnancy and the puerperium has shown a significant decrease. In the United States, at the time this Association was formed, the maternal mortality rate was seven times as high as it is today, just two decades later. This improvement is due to many factors: general improvement in medical practice as a whole, the discovery and increased use of chemotherapeutic and antibiotic agents, greater use of early and rapid blood replacement through blood banks, introduction and spread of postgraduate and refresher courses, increased hospitalization, training of the public in the realization of the benefits to both mother and child from early and adequate prenatal care, and, finally, the values derived from maternal mortality studies.

According to Dippel, "The woman who undertakes motherhood should travel the path of pregnancy, labor and delivery, and the puerperium without any ill effects, either to herself or the child; and her subsequent health should continue to be as good as before she conceived." To bring this about must be the aim of every obstetrician. Today the maternal mortality rates in many states are lower than what was regarded as the irreducible minimum ten years ago. In spite of this fact, recent well-conducted surveys indicate that many deaths are still preventable. In the 1950-1951 Minnesota Survey, where the actual coded rate was 0.51 per thousand live births, 45 per cent of the deaths were preventable, as judged by a committee of nine obstetricians when presented with all the available facts in each case.

The best and most thorough surveys have one or more investigators, trained in obstetrics and gynecology, who make immediate, on-the-spot investigations of each maternal death as soon as it is reported. They review the hospital charts and the nurses' notes, the anesthesia record, the pathologist's findings, and talk to all persons who came in contact with the patient. They go to the attending physician's office and obtain the entire history, including prenatal care, and discuss various points, to complete a detailed questionnaire. They also interview the consultants, and, if necessary, talk to relatives, adding to the previous history and the details of the pregnancy from the relatives' viewpoint. The investigators then write a summary of the case for presentation to the survey committee, which makes the final assessment in regard to: (1) the cause of death, (2) adequacy of care and conduct of the case, (3) the contributory or noncontributory factors with respect to prenatal care, labor and delivery, and postpartum care, (4) findings of the autopsy, particularly as to completeness, (5) accuracy of both the death and birth certificates, (6) possible preventability of the death, and finally (7) determination of the responsibility for the death, whether it be due to patient, hospital, doctor, disease, or any combination thereof.

Information obtained from the state and territorial health officers indicates that nineteen states and the District of Columbia are currently conducting maternal mortality surveys. A number of larger cities are carrying on local studies as well. In utilizing the information obtained from these sources I found that only five states and the District of Columbia conduct investigations of all maternal deaths based on the points just mentioned. The remaining states obtain

practically all of their information from the death certificate. A few of these do send out questionnaires to the attending physicians or hospitals to gain additional data.

It has long been known that many death certificates are inadequate, and in certain instances too ambiguous to be of value. The reports of various health departments and of the United States Bureau of Vital Statistics must, of necessity, therefore, be misleading. Proof of this can be demonstrated in reading analyses of thoroughly investigated cases, where a comparison is made between the reported cause and the actual cause of death. Furthermore, many deaths associated with pregnancy are not reported as such. During the latest Minnesota Survey nineteen additional deaths were uncovered—eleven of these by doctors and social service workers who were aware that a mortality study was being conducted, and eight by cross-matching the deaths of all women in the childbearing age against the birth certificates.

As the result of well-conducted surveys we can expect a further decrease in the maternal mortality rate. Every survey produces a good psychological effect upon the physicians and the hospitals in the area studied. The fact that the doctors are cognizant of the study makes them more careful, more conservative, and more likely to ask for earlier consultation. This has been definitely noticeable in the Minnesota studies, but one of the best examples may be seen in a Chicago survey. As the result of a maternal mortality study in the city of Chicago, a set of maternity rules was formulated at the request of the health commissioner and put into effect on Jan. 1, 1935. The adoption of the new rules was accompanied by an immediate drop in the maternal death rate from 4.3 in 1934 to 3.3 one year later. This was the largest single drop Chicago has ever had, and one of the committee members stated that the saving of at least half of the fifty-six lives salvaged that year was due directly to the installation of proper controls over all major operative procedures and all complications of pregnancy, labor, and the puerperium. Today the Chicago rate is less than 0.6 per thousand live births.

The maternal deaths in this country represent a considerable economic loss. For example, the coded maternal deaths in the United States in 1949 totalled approximately 3,500 mothers. The death of the mother dislocates the family group and is an important factor contributing to juvenile delinquency. Thus, the saving of maternal lives is of paramount value, not only materially, but socially and spiritually as well.

As a direct result of a mortality study, the members of the committee become aware of the use of unwarranted radical procedures and improperly administered anesthetics. In a recent survey there were four deaths due to faulty anesthesia. These deaths are not readily ascertained without a survey. As an example, one of the death certificates stated that the patient died of pneumonia. That was true. However, the record did not state that the pneumonia was precipitated by the aspiration of gastric contents due to an improperly administered anesthetic.

Furthermore, the survey will present the true picture regarding mortalities in various states and in smaller communities within each state. The use of faulty and dangerous procedures often becomes contagious within a community, and the members of the state committee have, through the use of a certain amount of finesse, a golden opportunity for correcting such practices.

Lessons learned from maternal mortality surveys can and should be used anonymously for educational purposes. The information so obtained furnishes excellent material for discussion in refresher courses or meetings of hospital staffs and county medical societies. These case reports are also extremely valuable for teaching purposes in our medical schools.

The conduct of a survey requires the complete cooperation of the members of the medical profession. It is best conducted by an interested group of obstetricians, working under the double banner of the state medical society and the state board of health.

Emerson, with his penetrating insight and gift for expressing truth, has advised, "Around every circle, another can be drawn." Realization by some states that they have achieved an acceptable maternal mortality rate does not rule out further study.

Good public relations mean education, both as regards the public's obligation in seeking early medical care, and, equally important, the earnest and continued efforts by members of our profession to improve the quality of that care. There are few other fields of medical endeavor which can be as proud of their progress as can the field of obstetrics, with its marked decrease in maternal morbidity and mortality. This accomplishment must stand as a challenge to all obstetricians in furthering the safety of motherhood in the future.

On Lake Superior lighthouses are a part of our daily panorama. They light the way for the mariner. I believe that maternal mortality surveys are lighthouses for the obstetrician. They warn him of the reefs of dangerous practices.

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THE SURGICAL MANAGEMENT OF CARCINOMA OF THE CERVIX*

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THE treatment of carcinoma of the cervix went from a surgical approach to that of radiation therapy because of the definite improvement in the five-year survival rates and the extremely low initial mortality in the radiated group, compared with those in the group who had been subjected to surgery. With the more radical surgical approach to malignancies in general, it was no more than would be expected that this very vulnerable lesion would be subjected to a revival of the old Wertheim operation. Bonney[1] in England, and Lynch[2] and Morton[3] in the United States continued to operate upon these patients, but, in 1944, Meigs'[4] report of his experience gave me the necessary stimulus to institute the radical surgical management in my cases of carcinoma of the cervix.

This paper represents the personal experience of the author in 100 cases of this disease, operated upon from Dec. 1, 1945, to July 1, 1951. It is obvious to everyone that the results from radiation treatment for these cases of carcinoma of the cervix still leave adequate reason for an improvement, and it is for that reason that I undertook this problem, and my results and conclusions will be given in this manuscript.

I agree with Meigs that this reasoning and our experience do not justify a plea for the universal acceptance of this extensive surgical procedure. On the other hand, however, if various clinics can offer an appreciable improvement in five-year survivals, then we shall rightfully have reason to promote more extensive institution of this treatment. To date, not enough cases have been followed five years to draw any solid conclusions, but, in a personal communication from Dr. Meigs, I am advised that he is reporting 74.1 per cent over-all, five-year survival in 85 true invasive cancers of the cervix upon which he operated five or more years ago. Dividing these into stages, we find that 80.7 per cent were Stage I (American College of Surgeons Classifications) and 60.7 per cent were Stage II. The radical operation done in this series, according to what I obtain from the literature, is definitely more extensive than the Wertheim operation, but, in addition to it, we have added the very extensive dissection of the gland-bearing areas, along with an extremely wide removal of the parametrial tissue and an adequate portion of the vagina, the amount depending somewhat upon the stage of the disease.

I do not believe that this procedure should be considered formidable. It is a difficult operation, in many cases, but any well-trained pelvic surgeon can learn to accomplish it. My operative mortality is slightly higher than that reported by others, but I have operated upon all ages and sizes of patients and I do not have a regular operative team, in itself a potent factor, and these three things alone have automatically increased the surgical hazards. I do not believe I should compare my results with those of cases treated by radiation,

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as reported by the best clinics in America and abroad, but rather with those of cases treated in my own community. This comparison I shall attempt to present, although no one realizes better than I do that a small series may cause distortion, one way or another.

It has been argued that general endorsement of this surgical management would cause an incompetent surgeon to subject his patient to an operation which would fall far short of a desirable dissection. This has occurred! I regret to report that we have seen patients, who thought they had had a radical Wertheim procedure, in whom the cervix was still present. However, the radiologist must not be too anxious to use this as an argument against the procedure, because we are all familiar with the inadequate and unpredictable radiation therapy which is today frequently used throughout the United States.

Material

The cases to be reported are shown in Table I. We have removed one of the early cases operated upon because it was proved four years later that the original diagnosis was incorrect. Another—an adenocarcinoma—has been discarded because it was established at the operation that the original lesion had been in the body of the uterus and had secondarily been implanted in the cervix. In order to retain unity in this report, I have also eliminated a patient who had had a maximum of radium and x-ray prior to surgery. I agree with Morton[3] that heavy irradiation contraindicated this radical dissection, because the ability of the tissues to establish collateral circulation has been so altered that urinary catastrophes would occur too frequently to warrant the recommendation. This leaves 92 cases which have been subjected to the Wertheim procedure and a small selected group of 5 patients who will be reported upon separately, 2 of whom have had a cystectomy with ureteral transplants and 3 who have had combined abdominoperineal resections in addition to the Wertheim operation.

TABLE I. MATERIAL. SCHMITZ CLASSIFICATION

Group I	15
Group II	47
Group III	30
Group IV	5
Total	97

Of the 100 patients operated upon, 73 come from the author's personal practice, 2 from a clinical service at Saint Anthony Hospital, and the remaining 25 from our Gynecological Service at the University Hospital in Oklahoma City. It becomes apparent at once that the other members of our Gynecological Department have not accepted the radical surgical treatment for their cases, because, if they had, we should have another 125 cases to include in this report. It also appears obvious that the physicians over the state of Oklahoma who have sent these 73 patients to my service must have done so because they have seen the poor results from the conventional type of treatment. I have not selected my cases as carefully as Dr. Meigs has done, and this fact would be reflected in a comparable report. I have operated upon all the patients coming under my care with the thought that the surgical procedure offered them a better chance of survival, regardless of size or age. However, I have arrived at some conclusions about this aspect which I shall mention later.

Classification

All of the biopsies from these patients have been reported as invasive carcinoma, and no carcinoma in situ has been included in this series. We have always used the Schmitz classification in our community, and therefore these cases are so classified, as demonstrated in Table I. I have made no attempt to establish a pathological grading, because the material has been reviewed by five different pathologists and their reports, like those of us clinicians, are rather confusing.

TABLE II. AGES

AGES (YEARS)	NO. CASES	PER CENT
20-30	14	15.21
31-40	36	38.04
41-50	17	18.46
51-60	17	18.46
61-70	7	7.60
71-80	1	1.08
Total	92	

Of the 20-30 year age group, only 1 is dead, 2 alive with disease, 6 alive and well 3 years postoperatively, 2 of whom showed positive glands.

Table II, which shows the ages of these patients who have been subjected to the surgical procedure, is of interest and is self-explanatory. The 15 per cent of the patients under the age of 31 years is very high, and their survival, as will be shown a few years later, may be a point in the decision as to whether or not this operation warrants continued use.

Of the 92 cases, 9, or 9.7 per cent, were columnar-cell carcinoma, and the remaining 83, or 82.3 per cent, were epidermoid in character.

Preoperative Preparation

Fortunately, most of the patients who are recommended for the procedure are in a good state of health and are not metabolic cripples, as are so often encountered in gastrointestinal or other surgery comparable with this procedure. However, we have, in cases as indicated, restored their blood to a normal level and corrected the blood chemistry. All of these patients receive Sulfathaladine in adequate doses to prepare the bowel so that it can be operated upon with some degree of safety, should it be inadvertently entered at the time of surgery or should more extensive surgery become necessary. They also receive penicillin the night before surgery and the next morning. They all receive Lipo-Cortical Hormone* the morning of surgery to counteract the reaction of alarm which is certain to take place after being subjected to this extensive operation. An adequate amount of blood is in readiness for the procedure.

The Operation and the Complications

The patient is taken to the cystoscopic room, and ureteral catheters are inserted just before coming to the operating room. We feel that this precaution facilitates the operative procedure and gives one a constant guard against ureteral damage. The anesthetic of choice is subarachnoid injection of Pontocaine, using glucose solution for the control of the height of the anesthesia and adding 0.25 c.c. of Adrenalin to the mixture, which usually will assure us of three to four hours of operative time. Intravenous Pentothal Sodium is usually given in just the amount necessary to keep the patient asleep and is extremely advantageous in taking away restlessness and prevent-

*The Upjohn Company.

ing large excursions of the diaphragm with the displacement of the intestines into the operative field after they have been carefully packed away. Three venous channels are established—two for blood and one for the Pentothal and glucose in water, but in which we can attach blood if the need arises. I have found myself embarrassed by relying on one vein with pressure equipment, only to find the blood infiltrating just at a critical time in the procedure. For the first 50 cases, I fairly routinely gave these patients 3,500 mg. hr. of radium, but I have abandoned that practice, because 40 per cent of these cases still showed carcinoma at the time of surgery, and I felt that the delay was not desirable. Furthermore, I am definitely certain that we are removing surgically a wider parametrial block than was being reached by the destructive rays from the implanted radium.

I shall not tire you by relating the steps in the procedure, believing it will suffice to say that the dissection which is done by me is apparently the Wertheim hysterectomy of old, plus the transperitoneal lymphadenectomy as carried out by the late Dr. Fred Taussig.[5, 6, 7] In one case, we severed the right ureter with a catheter in place. This was anastomosed together, and the patient still has a good, functioning kidney three and one-half years later. In two cases, we traumatized the branches of the sciatic nerve, in an effort to control hemorrhage, and, indeed, caused these patients some unnecessary pain. In one case, due apparently to the use of an improvised retractor, the right common iliac artery was completely severed just as it bifurcated into the internal and external branches. This was anastomosed together, and the patient has perfect circulation in her entire leg and foot ten months after the catastrophe.

The major technical difficulty in this procedure is the control of hemorrhage, and these patients receive from two to six pints of blood, with an average of 1,750 c.c. during the procedure. The obturator area is filled with veins of variable size, which bleed profusely when accidentally injured. We make an effort to clamp, sever, and ligate both ends of every vessel as we advance in the dissection. We may enter the obturator area by retracting the vein and artery medially or by going into it from below the vessels, just as the case seems to present itself. We use a suction tip for a blunt dissector and find it facilitates the procedure. The upper one-third of the vagina is removed along with the parametrium. It is closed with interrupted sutures, leaving an opening through which a double two-inch iodoform gauze is passed into the vagina, with each distal end extending out into the obturator and broad ligament areas on each side. This is removed on the fifth postoperative day. The pelvis is carefully peritonized after all bleeding has been controlled.

Postoperative Care and Complications

The immediate postoperative care is rather routine. They receive intravenous fluids every eight hours, adequate sedation, penicillin, and Lipo-Cortical Hormone. I had fully expected a high incidence of phlebitis, but to date we have had only one case.

Only the urinary complications remain as a serious concern, as shown in Table III. These patients frequently have trouble in emptying their bladders. Weeks and months go by before some of them have a normal sensation of natural micturition, although they are by that time emptying their bladders completely. We warn our patients of this before we remove the Foley catheters on the eighth or tenth day. The delayed urinary fistulas are the ones which continue to give us trouble. I have had six ureteral fistulas—three unilateral and three bilateral—5 occurring from the eighth to the sixteenth days postoperatively. The one which was a surgical accident and

another unilateral fistula healed without further treatment, and both patients have normal kidneys. I have done a ureterostomy in the other unilateral case, because I felt insecure to rely on her one kidney with an obstructed ureter, and did not sacrifice the kidney. The two bilateral cases—one in a 33-year-old patient and the other in a patient fifty-two years old—have both had bilateral ureterostomies, and both are getting along well. The other patient with a bilateral fistula, aged 54 years, is still to be treated, if it does not heal spontaneously. There have been two vesicovaginal fistulas, one of which healed spontaneously and the other necessitated a bilateral ureterostomy. A patient who has had urinary extravasation after a Wertheim hysterectomy cannot be considered as a fit subject for ureterointestinal anastomosis, leaving the uretero-cutaneous procedure the one of choice. These people are fitted with ureteral catheters which drain into a nonleaking collecting bag. All three of these women live on farms and perform their regular household duties.

TABLE III. COMPLICATIONS

	92 Operated upon	50 Irradiated
Ureterovaginal fistulas	6	0
Vesicovaginal fistulas	2	2
Cystitis	0	3
Rectovaginal fistula	1	0
Proctitis	0	4
Total	9 or 9.7%	9 or 18%

Two of the ureterovaginal fistulas healed spontaneously, one is still leaking, the other three have had ureterostomies. One vesicovaginal fistula healed spontaneously and the other has had ureterostomies. The rectovaginal fistula is in a 30-year-old patient, alive with disease, but causes her no inconvenience. Two of the three irradiation cystitis cases are bladder cripples. One irradiated patient has a colostomy and another has a marked constriction of the upper rectum.

The 8 cases (8.66 per cent) of fistulas remain too high but result from an attempt to do the operation adequately. Inasmuch as this complication did not occur in the first 35 cases I did, in which we routinely did presacral nerve resection, I am returning to this procedure in my future cases on the basis that this will prevent irreversible damage by eliminating vascular spasm. Collateral circulation in the older woman is frequently not enough to assure us against this complication.

Results

Out of these 100 cases reported here, there are 95 cases which have been subjected to the Wertheim hysterectomy and the Taussig lymphadenectomy, with two operative deaths, making an operative mortality rate of 2.1 per cent. One of these deaths was that of a large, fat woman who died from a cardiovascular collapse following the opening of an extraperitoneal abscess. The second death was that of a young woman of 31 years of age, who died from a blood transfusion reaction.

TABLE IV. RESULTS, 92 CASES

YEARS SINCE OPERATION	PATIENTS LIVING AND WELL	PATIENTS LIVING WITH DISEASE	DEATHS
5-6	8	0	1
4-5	7	0	4
3-4	10	2	2 (1 operative death)
2-3	17	1	1
1-2	18	1	1
Under 1 year	18	0	1 (operative death)
Total	78—84.6%	4—4.3%	10—10.8%

Table IV shows the outcome in these patients. The greater majority of this entire group of patients has received deep x-ray therapy after surgery. I have attempted to compare the group of patients operated upon the first two years of this series with those treated by radium and x-ray on our Gynecological Service at the University Hospital. The patients have been grouped equally to the best of my ability, and the comparison is exhibited in Table V. I have compared the patients operated upon during the first two years in this series. I carefully reviewed the charts of all patients with carcinoma of the cervix during the same space of time and attempted to classify them as I had in my own cases. Out of the 45 cases classified as Group III, I discarded 4 on account of inadequate treatment, one which had been treated elsewhere, and 14 cases which I thought either were Group IV cases or at least later than I would have subjected to this procedure.

TABLE V. COMPARISON OF RESULTS BY OPERATION TO THOSE TREATED BY IRRADIATION (DEC. 1, 1945, TO DEC. 1, 1947)

METHOD OF TREATMENT	GROUP (SCHMITZ)	3½ TO 5½ YEAR CASES	PATIENTS LIVING	PER CENT
Operation.—	I	4	4	100
	II	12	10	83.3
	III	8	5	62.4
	Total	24	19	79.1
Irradiation.—				
	I	9	8	88
	II	15	12	80
	III	26	8	30.7
	Total	50	28	56

In addition to these 92 cases, there is the small group of five patients who have been subjected to additional surgery as a curative measure and not as wholly palliative (Table VI). The outcome of these five selected patients makes this procedure worthy of our consideration. Three of these patients have had a combined abdominoperineal resection in addition to the Wertheim procedure. One is living, is well, and is managing her restaurant, three and one-half years following her surgery. She not only had an extensive metastasis to the posterior vaginal wall and rectum but metastatic glands in the right and left internal iliac glands. One, with an adenocarcinoma, is alive but with recurrent disease. She had metastatic lesions in the ileum, requiring an intestinal resection, and metastatic glands in every area dissected. The other patient is almost a year past her surgery and has had an extensive lesion on the posterior vaginal wall, infiltrating into the pararectal structures. The patient on whom we did a cystectomy with ureterointestinal anastomosis died in the hospital, but the other on whom we did a cystectomy and a bilateral ureterostomy after a Wertheim dissection is alive and well and back at her job as a telephone operator, although she was operated upon only nine months ago.

TABLE VI. GROUP IV, SCHMITZ CLASSIFICATION

PATIENT	AGE (YEARS)	DATE	OPERATION	RESULT
E. S.	57	2/ 3/48	And abdominoperineal resectian	Alive and well
J. V.	48	7/25/49	And cystectomy with ureterointestinal anastomosis	Hospital death
N. T.	42	10/12/49	And abdominoperineal resection Resection of 18 inches of lower ileum	Alive with disease
V. B.	43	10/11/49	And abdominoperineal resection	Alive and well
E. G.	36	1/29/51	And cystectomy and ureterocutaneous anastomosis	Alive and well

Comment

This review dates back five and one-half years and represents a series of patients who have been given a chance to make their own decisions. In all my private patients not one has chosen to deny herself the proposed surgical procedure. Likewise, every doctor who has referred a case to me has been consulted about the proposed therapy and has been agreeable to this method of treatment before such treatment was instituted.

We have not had a single case of more than fleeting x-ray reaction, while in this two-year follow-up at the University Hospital there are two patients living who are urological cripples from x-ray reaction. Another has continuous symptoms from a radiation proctitis, and another has a constriction in the rectum, which the proctologists interpret as the result of her radiation, while another has had a colostomy.

The most striking fact about this group of people is their emotional stability and their certain attitude of being cured. There is not that tremendous element of doubt in their minds that there has been in the minds of my patients formerly treated totally with radiation. The tumor has been removed and they are well! This difference is so striking that, in itself, it adds to the other reasons why I am still optimistic about this surgical management of carcinoma of the cervix.

If it were not for the urinary complications, this procedure could not be considered as a serious operation. The accidents are apparently becoming more frequent as we extend our dissection a little farther. The incidence is definitely too high, but the patients in this series who have a permanent handicap are all grateful to me that they are still alive. They are comfortable and in no way can be compared with those whose bladders have been harmed by radiation.

I am watching three girls whose malignancies were associated with pregnancies. I am also, at this time, very optimistic over the survival of the five patients with carcinoma in the cervical stump, all of whom had plenty of cancer at the time of their surgery.

The 15 cases, as shown in Table VII, in which glandular metastasis has been found, have not been regrouped. This group likewise bears our closest observation, because no one has yet proved that he has sterilized a gland with x-ray treatments in which metastatic cancer was present. One of the 6 patients operated upon before Sept. 1, 1948, in whom metastatic glands were found, died at the end of fourteen months, one is alive with disease four years after her surgery, and the other 4 are alive and well four years and two months, three years and ten months, two years and eight months, and three years and one month, respectively, after their metastatic findings had been established.

TABLE VII. POSITIVE GLANDS

	NO. CASES	PER CENT
Positive glands	15	16.3
Positive glands, dead	2	13.3
Positive glands, alive with disease	2	13.3
Positive glands, alive and well	11	73.3
External iliac 0 cases, internal iliac 12 cases, obturator 3 cases, ureteral 3 cases		

The two patients who are dead had recurrences under one year following surgery. One, Group II, living with disease 4 years following surgery, developed recurrence 10 months after operation. The other, Group III, living with disease 3 years after surgery, developed symptoms of recurrence 2½ years after operation.

Conclusions

1. This group of 95 cases, with two deaths, demonstrates that carcinoma of the cervix can be treated by radical surgery with a very low mortality.

2. The urinary complications are too frequent at 8 per cent, but this area must be dissected if we are to consider this an adequate surgical approach. I hope to reduce its frequency by reinstituting a presacral neurectomy.

3. I have continued to give deep x-ray therapy and believe that I am not denying these patients anything that they have formerly been receiving but have added to our therapeutic armamentarium.

4. The satisfied state of mind that these patients have toward their longer life expectancy is a very valuable adjunct to their future lives.

5. The patient past 60 or even younger, if in a poor state of health, should be carefully investigated, and, if there is a question as to her vascular system, she probably should not be operated upon, and the patient who has had a maximum amount of irradiation should be denied surgery, because, in these patients the urinary complications are too high.

6. I believe that the Wertheim hysterectomy with a transperitoneal bilateral lymphadenectomy has a place in the treatment of carcinoma of the cervix.

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Discussion

DR. CLYDE GEIGER, Chicago, Ill.—In the last decade there has been, in certain clinics, a noticeable increase in the popularity of surgery as a method of treating selected cases of invasive cervical cancer. However, it is generally agreed that radium and roentgen irradiation properly administered is still the treatment of choice. Surgery, if used, should not be confused with the so-called Wertheim hysterectomy. Brunschwig and Meigs emphasize that the operation they perform today is much more radical and that the name Wertheim should be forgotten and the procedure be called "radical hysterectomy with bilateral pelvic lymphadenectomy." In this procedure, as Meigs states, "An attempt is made to remove so far as possible all the lymph nodes, lymph channels, and fat from the common iliac artery down along the whole arterial and venous tree into the pelvis, beneath the bladder, around the rectum, into the obturator fossa." He also removes the parametrial tissue over to the lateral bony wall and the upper one-half of the vagina.

Dr. Kelso has presented a review of 100 patients who were subjected to a Wertheim hysterectomy with removal of the regional lymph nodes. It might be of interest to know if his operative procedure is as extensive as performed by Meigs and Brunschwig. Two cases were discarded because they were later proved not to be cervical cancers and a third was omitted because the patient received a maximum of x-ray and radium therapy before surgery. Five patients had partial pelvic exenterations and will be discussed separately—thus 92 cases are included in this statistical study. In the first 50 cases 3,500 mg. hr. of radium was used preoperatively but this procedure was discontinued because 40 per cent of the cases still showed evidence of carcinoma at the time of surgery. This is to be expected because 7,000 gamma

roentgens are generally accepted as a cancerocidal dose. As to the surgical removal of a wider parametrial block than was being reached by the destructive rays from the implanted radium, this would be anticipated because the rays from radium are effective for a distance of only 3 cm. from the source. Deep x-ray therapy is used for the control of parametrial spread which was also used postoperatively in the majority of the author's cases.

This review covers a 5½ year period from Dec. 1, 1945, to July 1, 1951. However, as noted in Table IV, there are 25 patients operated on 3 years ago or longer and only 8 cases over 5 years ago.

It is interesting to note in Table II that there were 14 patients who were between 20 and 30 years of age. The average age incidence for carcinoma in situ is 36 or 37 years. Meigs in a recent report before the American Gynecological Society (May, 1951) deleted 15 of the 100 patients operated on 5 or more years ago for cervical cancer after a review of his material by a group of pathologists. They classified 13 cases as preinvasive carcinoma and two as endometrial carcinoma. It might be of value for the essayist to rereview his slides, especially in the younger age group.

In order to evaluate radical surgery as a method of treatment for cancer of the cervix the following questions should be answered: 1. What is the operative mortality? 2. Is the procedure easy or difficult to perform? 3. What injuries or complications can occur? 4. What percentage of cases are suitable for this procedure? 5. What is the clinical result or salvage? A comparative analysis should then be made with the radiation method of treatment.

Dr. Kelso reports a 2.1 per cent operative mortality in 92 cases. However, there was one death in the 5 cases of partial pelvic exenterations which is not included. In other words, there were 3 deaths in 97 cases, or 3 per cent. A more careful selection might have reduced this mortality since one death was in a large fat woman. Twombly recently stated, "It has become increasingly apparent that obesity is a contraindication to radical hysterectomy." In 100 selected cases Meigs had no mortality. Jordan states that at Memorial Hospital, in 300 relatively unselected cases, there was a 1 per cent mortality. Pratt from the Mayo Clinic recently reported a 4.4 per cent hospital mortality but no operative death since 1943. However, this radical procedure certainly could not be performed by a less experienced surgeon without a much higher risk. Irradiation therapy properly administered should have less than a 1 per cent mortality and this can be further reduced by the use of antibiotics, adequate nutrition, and blood transfusions.

Because of the difficulty in doing this radical procedure many incomplete dissections will be done by unqualified surgeons, as Dr. Kelso states he has seen. This is reflected in the increasing number of recurrences following incomplete surgery that are seen in cancer clinics in recent years. This has been our experience at the Cook County Gynecological Tumor Clinic. As stated by Corscaden, "unless the dissection is thorough it is actually worse than useless."

The incidence of operative injuries, as noted in Table III, of 9.7 per cent is high but this is to be expected with a radical procedure of this type—especially bladder and ureteral injuries which were present in 8 of the 9 cases. If the ureter is not well cleaned cancer tissue will be left behind. On the other hand, if the ureteral sheath which carried the blood supply is removed for a short distance or severely damaged the ureter will slough with a resulting fistula. Meigs has discontinued the use of catheters in the ureters during surgery because when the ureter is picked up with tissue forceps it compresses the lining of the ureter against the hard catheter and causes more ureteral damage. His incidence of ureteral complications has decreased since he discontinued this practice. Pratt reported an incidence of 4.4 per cent ureteral and bladder injuries. Preoperative irradiation may increase the incidence of bladder and ureteral fistula slightly; however, Meigs noted an incidence of 16.7 per cent ureteral vaginal fistula in his nonirradiated group and 7.4 per cent in the irradiated group. Unless the operator is well trained in radical pelvic surgery the operative injuries especially of the urinary tract will increase a great deal. The number of irradiation injuries was also 9, of which cystitis and proctitis accounted for 7. At the present time the incidence of permanent urinary and intestinal injuries due to properly administered irradiation should be minimal.

It is rather surprising that there were not more clinical Group III and IV cases operated upon since the essayist states he "operated on all the patients coming under my care." It has been our experience to see a greater number of advanced cases than the author reports. Usually only about 15 to 20 per cent of all cases seen are suitable for surgery because of obesity, age, physical status, and clinical extent of the disease. With irradiation nearly all cases can be treated.

Evidence has been presented by the studies of Morton and Henriksen that lymph nodes invaded by carcinoma do respond to radiation. Furthermore, the survivals in Stages II and III would seem to substantiate this view.

Evaluation of results in a small series of cases with insufficient time for a five-year follow-up is inconclusive. For example, there were 4 clinical Group I (Schmitz) surgically treated patients. Assuming one patient does not survive 5 years then the salvage rate would be 75 instead of 100 per cent. With irradiation Schmitz reports a 92 per cent survival.

With reference to Meigs' 82.1 per cent over-all five-year survival in 100 cases, it is of interest to note that this figure had been reduced to 74.1 per cent since 15 patients have been excluded. Meigs survived in his selected Stage I (International classification) cases is 80.7 per cent which is comparable to the results with irradiation as reported by McKelvey (81.1 per cent), Schmitz (77 per cent), and Castolow (83 per cent) in unselected Stage I cases.

Surgery is indicated whenever the cervical lesion does not respond favorably to irradiation. Unfortunately, the radiation resistance or radiation sensitivity of the tumor cannot be evaluated before treatment has been instituted. During the course of treatment vaginal smears and interval biopsy studies usually will indicate whether the tumor is resistant or not.

Recurrences occurring in adequately radiated cases should also be subjected to surgery, if sufficient time has not elapsed to warrant reirradiation.

Evidence has not been presented up to the present time to show that radical surgery properly performed is superior to properly administered irradiation. The reported operative mortality, bladder and ureteral injuries, and recurrences due to incomplete dissections will increase in the hands of a less experienced surgeon.

DR. GEORGE KAMPERMAN, Detroit, Mich.—I am greatly amazed when I read of the type of surgery that is now being performed for carcinoma of the cervix. It is amazing to me because there was a time in my career when I was associated with Dr. Reuben Peterson, during which time he was trying to do this same thing, trying to find a way of doing something for patients with carcinoma of the cervix. That period was from 1907 to 1912.

Probably it isn't fair to compare the surgery of today with then, because the surgery of today is entirely different from what it was then. We didn't have the expert anesthesia that we have now; we didn't have any antibiotics; we didn't have blood transfusions; we didn't know anything about intravenous glucose. If a patient went into shock, the only treatment we had was salt solution, hypodermoclysis.

At that time we had a series of 52 Wertheim hysterectomies. We had a primary mortality of 19.6 per cent. Those 52 patients who were operated upon represented one-fourth of all the cases that showed up in the clinic. The entire series represented 208 cases, and it was considered that just 52 of those were operable, that is, one-fourth of all the cases presented were considered operable.

At that time every operation performed was undertaken with the idea that it was an exploratory, and, if the condition was suitable, the operation was performed. That was the general tendency at that time.

Of the 52 patients that we operated upon, 25 per cent had five-year survival. At that time we had no radium and no adequate x-ray therapy, so this was an encouragement. Upon reflection, however, we felt this way: We operated on one-fourth of the cases, and one-fourth of those operated upon survived. This means that one-sixteenth of the entire series, between 6 and 7 per cent, was all we could salvage. All other treatment was palliative with no idea or hope of a cure.

When radium and x-ray began to be used we soon found we could get a better result with radiation.

I might add that at Harper Hospital we treat practically all of our cases with radium and x-ray. We use preliminarily a 5,000 mg. hr. dose of radium, and follow with x-ray therapy by the supervoltage method. Six weeks later they receive radium again, this time 3,200 mg. hr., and again they have a series of x-ray treatments. As a result we have a survival rate of almost 39 per cent. We now have a hope of curing some patients we formerly treated only palliatively.

We keep our statistics a little differently from the way many others do. We have a record of all patients applying for treatment. They are then our cancer cases. They are then treated. A good number of them do not finish the treatment. After one dose of radium they quit, or they stop some time during the course of treatment. Even those evidently incurable, with frozen pelvis, are included in our series. Nevertheless, they are our cancer cases, and when we say 38 to 40 per cent survive we mean 38 to 40 per cent of all the patients who apply for treatment, whether they finish our treatment or not, or whether we treat them or not.

I would like to ask Dr. Kelso this: In his series of cases, how many cases are there that he did not operate upon? Surely he must have had a good many cases of Group IV, frozen pelvis, upon which he did not operate. I am curious to know what percentage of the cases were really salvaged.

Those that were operated upon were considered operable, and naturally the results are fairly good. But when you class the whole mass of patients together, all the cancer patients, how many did he salvage? With our radium and x-ray at Harper Hospital we feel we salvage from 38 to 40 per cent.

I am glad to stand on the sidelines and watch the experts do it. I feel that this should not be considered as a definite treatment for carcinoma, but should be done as a piece of research work. When we have men who can do these operations well, and when we let them do this work, they will soon show us whether or not this piece of research is showing results.

We should be very careful to emphasize the fact that this is not an operation for everybody. General surgeons should not do it, nor by any means all the gynecologists. A few men can do this operation and can do it well, and with them it should be a piece of research work. Maybe if they take that attitude, and not assume it is the only cure, we will find it is helpful.

DR. HARRY M. NELSON, Detroit, Mich.—As Dr. Kamperman has said, I think surgery of carcinoma of the cervix should be regarded as surgical research. Institutions such as Memorial Hospital in New York, which for the present regards cancer of the cervix as a surgical problem, are perhaps doing a very good piece of research, in that eventually they will give us some statistics worth while.

However, I do believe it is wrong for our schools and some of our hospitals to teach their residents and their students that carcinoma of the cervix is a surgical problem. Many students today are going out and stating that carcinoma of the cervix has become a surgical problem. Certainly radiotherapy has produced as good results as has good surgery.

There has been as much progress in research in radiotherapy as there has been in surgery. As a matter of fact, I believe most of the radiotherapists today are much better prepared to treat carcinoma of the cervix than is the average gynecologist and the average surgeon. Therefore, taking the country as a whole, I am sure that our patients with carcinoma of the cervix will get better care if they are put in the hands of good radiotherapists than they would get by being put in the hands of the occasional operator for carcinoma of the cervix.

DR. KELSO (Closing).—I do not believe that this problem should be considered a feud between radiologists and surgeons; instead, it should be thought of as an effort toward a decision as to the most logical management of this disease. The statistics from our University Hospital, as given in this report, are not good, but they are accurate. It is important to remember that all my patients cannot go to distant cities for their treatment, and that, consequently, we must adapt our treatment to their needs, offering them the best procedure possible in our own localities. I have presented this comparison for your consideration.

In my paper, I state that the point has been made that this operation would soon bring inadequate dissections by unqualified operators. This it has done. I have seen a patient, who

thought she had had a radical Wertheim hysterectomy, whose cervix was still present. I do not believe the radiologists should consider this situation as an argument wholly in their favor, because I can always write to a rental company in Chicago or New York and secure radium ready for application. I am sure that the best result obtained by the occasional doctor using radium acquired from either of these sources would not be equal to the surgery which might be done by any man here this morning.

I cannot answer Dr. Kamperman's question as to the ratio of operable cases to inoperable ones in this series, because these patients have been sent to me by doctors throughout the state of Oklahoma and from near-by sections of Texas. There is no way to estimate the number of advanced cases these men saw in this same period of time.

We teach our medical students that the acceptable management of carcinoma of the cervix today is radium and x-ray, and we thoroughly explain to them that the Wertheim hysterectomy, plus the Taussig lymphadenectomy, is a surgical investigation, and that, until some solid conclusion is reached, they are to continue to treat their patients with radiation.

I can assure you that I have accepted this challenge as a surgical research problem, and I think it should be considered in that light. However, with the surgical advancements and the surgical liberties afforded us by perfect anesthesia, blood replacement, and the antibiotics, there are more men, I believe, who can train themselves to do this operation than there are good radiologists in the United States today.

If in another five years we are able to report to you a survival rate comparable to that estimated in this review, I believe there will then be general acceptance of the procedure, regardless of the surgical hazards.

ANALYSIS OF FETAL MORTALITY IN CESAREAN SECTION. EXPERIENCE IN AN URBAN COMMUNITY*

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THE downward trend of fetal mortality in cesarean section during recent years has not kept pace with the sharp drop in maternal mortality. A review of 763 consecutive sections done in an urban community showed 115 infant deaths per thousand abdominal deliveries, as opposed to 39 per thousand for all deliveries. Analysis was made to ascertain the relation of inappropriate or poorly timed application of abdominal hysterotomy to fetal mortality. The study is presented with the opinion that conditions in this community probably are representative of conditions in other parts of the country.

Material

Data were collected from all six civilian hospitals serving Knoxville, Oak Ridge, and Maryville, Tenn. In the first two communities, the period of study extended from Jan. 1, 1948, to June 15, 1950, and in the third instance, from Aug. 1, 1947, to April 1, 1949.[2] Information was obtained from the record libraries and delivery room rosters of the various hospitals and the Department of Public Health of the City of Knoxville, Tenn. The hospitals are designated by letters A to F.

Hospitals

Each hospital was equipped with a maternity unit, isolation nursery, and blood bank. A majority of parturients admitted were private patients, the others were indigent and treated largely in one hospital (B).

Staff

Five hospitals have open staffs while the sixth (A) has a closed staff. The sixth has a department of obstetrics and gynecology that is supervised in a manner comparable to that in a teaching hospital. Here, most of the obstetrics is done by physicians who limit their practice to obstetrics and gynecology. Much of the medical care is administered by residents and interns under the direction of an attending staff in a second hospital (B). Patients are cared for by their own physicians and there is no direct supervision of the maternity division in the remaining four hospitals.

More than one-third of the physicians in the community, or about 100 practitioners, give some obstetric care. Nine physicians limit their practice to obstetrics or to obstetrics and gynecology.

The staff in one hospital (A) review their obstetric problems each month in an effort to improve their standards of care. Standards are controlled indirectly and ineffectively by a record committee in a second hospital (C). There

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is no demonstrable control in the other four institutions, other than that a signed consultation is required. In all hospitals, with one exception, consultation often is requested and given without regard to obstetric training or even obstetric practice, occasionally only as a mere administrative favor without observation of patient or review of record. Contrariwise, in the excepted hospital (A), it usually is given as a critical analysis by one or more experienced obstetricians.

Operators

Cesarean sections are done by obstetricians in the hospital with the lowest incidence of abdominal delivery. Contrariwise, only one-fourth of the procedures are done by obstetricians in the hospitals with the highest incidence. The other three-fourths are performed by general surgeons and general practitioners.

TABLE I. INCIDENCE OF CESAREAN SECTION

HOSPITAL	TOTAL BIRTHS	CESAREAN SECTION	PERCENTAGE OF TOTAL
A	2,213	37	1.6
B	3,256	90	2.8
C	1,762	66	3.7
D	2,758	126	4.6
E	1,934	97	5.0
F	4,634	347	7.5
Total	16,557	763	4.6

Incidence

The incidence of cesarean section, given in Table I, varied from 1.6 to 7.5 per cent in the different hospitals. The institution with the best regulated maternity division had the lowest incidence. In contrast, the hospitals with the least departmental supervision had the highest incidence.

Indications for Section

Reasons for abdominal delivery are given in Table II. Over one-fourth of the women had experienced previous cesarean section, and of these one in 18 suffered complete or incomplete uterine rupture. This complication emphasizes a subsequent hazard of the operation and accentuates the importance of a reasonable justification for the first hysterotomy.

Cephalopelvic disproportion was ill defined in more than two-thirds of the women with this diagnosis. X-ray mensuration and mechanical methods for pelvic evaluation were unrecorded in many instances, while in others the designation, disproportion, appeared questionable, as where an immature infant was born to a woman with either normal pelvic measurements or previous history of having normal-sized babies by the vaginal route without apparent difficulty.

Under the heading, previous hard labor or stillbirth, clinical evidence was not given to prove the presence or absence of pelvic dystocia.

Not uncommonly the diagnosis of placenta previa was established neither before nor after operation.

Nearly one-sixth of the women laparotomized for toxemia had or recently had had eclampsia. One-fourth of those with supposed uterine inertia apparently were not in active labor; none of them had cervical dilatation as determined by rectal or vaginal examination.

Included under the "all other" indication were previous phlebitis, hyposthenia, previous postpartum bleeding, previous peptic ulcer, election by patient, postmaturity, hydramnios, epilepsy, and hydronephrosis. In general, these did not appear to be legitimate indications.

TABLE II. INDICATIONS FOR CESAREAN SECTION

INDICATION	PATIENTS* NUMBER	PERCENTAGE OF TOTAL
Previous section (12 with ruptured uterus)	213	28.0
Disproportion	134	17.6
Toxemia (8 eclamptic)	78	10.2
Placenta previa	52	6.2
Uterine inertia	40	5.2
Abruptio placentae	38	4.9
Previous difficult labor or stillbirth	35	4.6
No data	32	4.2
Breech	20	2.6
Primipara, 35 years old or more	19	2.5
Abnormal presentation	17	2.2
Fibroid uterus	16	2.2
Previous vaginal plastic operation	9	1.2
Heart disease	7	0.9
Twins	7	0.9
Unable to deliver with forceps	5	0.7
Sterilization	5	0.7
Elected by the physician	5	0.7
Prolapsed cord	3	0.4
Cervical stenosis	3	0.4
Hydrocephalus	3	0.4
Diabetes mellitus	2	0.3
All other	38	5.0

*Some women had more than one indication.

Maternal Deaths

Four maternal deaths occurred, one each from infection, ruptured uterus, pulmonary edema following treatment with intravenous fluids given for shock from abruptio placentae, and mismanagement in a central previa. Eleven other women suffered varying degrees of uterine rupture and survived.

Incidence of Fetal Mortality

There were 753 single and 10 twin births. Six hundred sixty-four babies were discharged alive, 88 died, and data for 21 were unknown.

The incidence of fetal mortality is given in Table III. Compare the fetal mortality rate of 81 to 200 per thousand (average 115) abdominal deliveries to the gross fetal loss of 29.5 to 68 per thousand (average 39) for all deliveries in the various hospitals. In other words, with the average fetal loss of three to one, the conclusion must be made that laparotomy does not necessarily insure a living infant.

TABLE III. FETAL MORTALITY

HOSPITAL	TOTAL SECTIONS	INCIDENCE SECTION	FETAL DEATHS	FETAL MORTALITY PER 1,000 ABDOMINAL DELIVERIES
A	37	1.6	3	81
B	90	2.8	18	200
C	66	3.7	8	121
D	126	4.6	12	95
E	97	5.0	9	93
F	347	7.5	38	109
Total	763	4.6	88	115

Responsibility for Fetal Loss

Delivery of a known dead infant by cesarean section is usually unnecessary. Yet, in this study, nearly half of the babies were dead before the operation was begun. The others died either during operation or neonatally.

For purposes of discussion, cesarean section in relation to fetal deaths was evaluated under four headings: justified, unjustified, poorly timed, and questionable or controversial.

Twenty-one sections were considered justified for maternal reasons even though all babies died. See Table IV. The procedure for uterine rupture, cervical cancer, and Pott's disease requires no comment. Bleeding due to abruptio placentae was acute, severe, and associated with a closed cervix. Where previous section was the indication, one baby died of erythroblastosis, and the clinical course of two others, who were mature, suggested atelectasis. Fetal death with transverse presentation apparently was due to anoxia secondary to inhalation anesthesia, aspiration of amniotic fluid during birth, or both, because the fetal heart was normal and the patient was not in labor prior to operation. The previas were either central or of the lateral type with active bleeding and closed cervix. The disease, among women with nephritis and toxemia, was becoming progressively worse in spite of active medical treatment.

TABLE IV. CESAREAN SECTION CONSIDERED JUSTIFIED

INDICATIONS FOR SECTION	STILLBIRTHS	NEONATAL DEATH
Ruptured uterus	6	0
Abruptio placentae	3	0
Previous section	0	3
Transverse presentation	2	0
Placenta previa	2	0
Toxemia	1	1
Cervical cancer	0	1
Pott's disease	0	1
Nephritis	0	1
Total	14	7

Laparotomy was regarded as unjustified in 22 patients (Table V). Infants of five women with abruptio placentae were premature and weighed less than 2,000 grams; three of these less than 1,500 grams. In each instance, bleeding was neither of sufficient quantity nor uncontrollable to the extent that abdominal delivery be done for maternal reasons. The hydrocephalic baby weighed only 2,600 grams. Babies of patients with polyhydramnios were of average term size. One of the hypertensive women had a macerated stillborn infant. She had not felt fetal movements for several days. A second toxemic patient was in early labor and a third was untried on medical treatment. The second and third had babies weighing 1,800 and 1,400 grams, respectively. All babies identified under the designations, twins, disproportion, premature rupture of the membranes, and marginal previa weighed less than 1,800 grams. Women with twins apparently were in labor. Those with supposed uterine inertia presumably were not in active labor for none had any cervical dilatation. All their babies were premature. The stillborn, breech baby weighed 3,040 grams. The mother was not in labor and there was no recorded cephalopelvic disproportion or other complication. The woman who gave birth to the erythroblastotic baby was a multigravida and had a normal pelvis.

Cesarean section was poorly timed in relation to the expectation date or to treatment for a complication in cases where 19 babies died (Table VI). Those who died, where indication was previous section, weighed less than 2,500 grams; most of them weighed under 2,000 grams. Deaths associated with placenta previa were usually of babies who weighed less than 1,750 grams. Expectant treatment was not utilized and bleeding was mild. On the assumption that laparotomy is the procedure of choice for toxemic mothers, the macerated stillborn infant indicated, in one instance, that the operation was deferred too

long. In the second instance, it was not delayed long enough; the mother was eclamptic. Prolonged labor antedated hysterotomy done for transverse presentation and pelvic dystocia. The tuberculous patient had a baby weighing only 1,750 grams.

TABLE V. CESAREAN SECTION CONSIDERED UNJUSTIFIED

INDICATIONS FOR SECTION	STILLBIRTHS	NEONATAL DEATH
Abruptio placentae	3	2
Anomaly or polyhydramnios	2	1
Toxemia	2	1
Uterine inertia	1	2
Twins	0	2
Pelvic disproportion	0	2
Premature rupture of membranes	0	1
Placenta previa	0	1
Breech presentation	1	0
Erythroblastosis	1	0
Total	10	12

TABLE VI. POOR TIMING OF SECTION AND FETAL DEATH

INDICATIONS FOR SECTION	STILLBIRTHS	NEONATAL DEATH
Previous section	1	8
Placenta previa	2	3
Toxemia	1	1
Pelvic dystocia	1	0
Transverse presentation	1	0
Pulmonary tuberculosis	0	1
Total	6	13

Data were too incomplete, or factors leading to section were considered too controversial, to give a definite opinion as to the advisability of abdominal delivery in 26 instances (Table VII). Nearly half of the babies were premature. The others either were mature or the size was recorded as near term without a weight being given. Most of the premature infants were seen in cases where section was done for abruptio placentae. The stillborn infants, where the indication was previous section, were mature and the pregnancies apparently normal. The baby in transverse presentation weighed 1,800 grams and the one classified under the indication, disproportion, weighed 2,580.

TABLE VII. SECTION QUESTIONED IN RELATION TO FETAL DEATH

INDICATIONS FOR SECTION	STILLBIRTHS	NEONATAL DEATH
Abruptio placentae	8	3
Placenta previa	3	1
Toxemia	2	4
Previous section	2	0
Pelvic dystocia	1	0
Transverse presentation	0	1
Pelvic disproportion	0	1
Total	16	10

Prematurity

There were 123 premature infants, 629 mature, and the size of 21 babies was unknown. Babies who weighed 2,500 grams or less were considered premature. Over 40 per cent of the prematures were lost as opposed to nearly 60

per cent saved. Corresponding figures for mature babies were nearly 5 and 95 per cent.

The incidence of prematurity for all births ranged from 5 to 12 per cent in the various hospitals. Corresponding figures among babies born by section were 6 to 30 per cent. Over one-third of the premature infants in the study weighed less than 2,000 grams; the others weighed 2,000 to 2,500 grams or the exact size was unrecorded.

Fetal age at operation is given in relation to fetal death in Table VIII. Note that the majority of these infants were premature.

TABLE VIII. FETAL AGE AT OPERATION

INDICATIONS FOR SECTION	PREMATURE	MATURE	UNKNOWN
Placenta previa	12	1	0
Abruptio placentae	10	7	3
Toxemia	9	2	2
Previous section	8	4	1
Uterine inertia	2	1	0
Cephalopelvic disproportion	2	1	0
Transverse presentation	1	3	1
Ruptured uterus	1	5	0
All others	5	7	0
Total	50	31	7

Assigned Cause of Fetal Death

The assigned cause of fetal death is given in Table IX. Anoxia was assigned in instances of uterine rupture, abruptio, prolonged labor antedating section, and in cases where anesthesia or aspiration of amniotic fluid theoretically caused fetal death.

TABLE IX. CAUSE OF FETAL DEATH

CAUSE	STILLBIRTHS	NEONATAL DEATH
Prematurity	7	34
Anoxia	28	0
Unknown	5	6
Toxemia of mother	2	0
Anomaly	2	1
Erythroblastosis	2	1
Total	46	42

Comment

Forty out of 88 fetal deaths occurred with improper timing or inappropriate use of cesarean section. Undoubtedly there were patients who had vaginal deliveries who should have been treated by abdominal hysterotomy but data on that phase are outside the scope of this paper.

Fifty out of 81 babies of known size who died were premature, indicating that prematurity was a common problem.

Most would agree that fetal salvage with elective, uncomplicated hysterotomy for the indication, previous section, should approximate results with uncomplicated vaginal delivery. In this study nearly one-fourth of the neonatal deaths came in this category and the majority of these babies were premature. Hydrocephalus, polyhydramnios, and false labor, misinterpreted as uterine inertia, were regarded as unjustifiable reasons for elective section. The same is true where cephalopelvic disproportion was applied in terms of a term infant to a premature. A woman who is to be laparotomized for cephalopelvic dispro-

portion is entitled to x-ray evaluation. On the contrary, obstetricians should not fall into the trap of always taking the roentgenologist's opinion verbatim, as was occasionally done in this experience. Mechanical and x-ray pelvimetry, no matter how accurate, do not always give in advance of labor appreciation of the size, shape, and moldability of the fetal head, the effectiveness of uterine contractions, the exact expectation date, and the thickness and tension of soft structures. The procedure should be used as an aid to elect a method of treatment.

We call attention to the article on the management of antenatal hemorrhage by Fish, Bartholomew, Colvin, and Grimes.[1] We are convinced, as they are, that conservative treatment with rupture of the membranes, drainage of the amniotic fluid, and subsequent vaginal delivery is usually preferable to cesarean section in the case of most patients with abruptio placentae, not only because of the immediate risk, but also for future risks in childbearing. Munro Kerr[6] employed this treatment for abruptio, even before blood banks were known, without undue maternal hazard. Fritz Irving[8] introduced the teaching in Boston in the thirties. Experience teaches that the outlook for the baby in this situation ordinarily is poor and treatment based on only fetal indication usually is inadvisable. There are those who undoubtedly will differ with this opinion. But a recent study at New York Lying-In Hospital showed cesarean section did not improve fetal salvage among women with abruptio; the loss was 54 per cent with section. Our loss, where section was done for practically all degrees of premature separation, was 53 per cent. It is important to remember that patients with abruptio are often toxic, in shock, and are poor surgical risks. Yet these same women usually have tonic uteri that will empty themselves, if treatment is given as previously described.

Intelligent, expectant treatment for painless uterine bleeding, until the baby becomes of viable size, has been practiced, principally by Herman Johnson[7] and the late Tiffany Williams,[9] long enough to demonstrate that it does not increase maternal mortality. Maternal deaths generally come from improper treatment. Abdominal delivery is usually unnecessary in marginal previas and even in some lateral previas.

Conservative treatment in abruptio and expectant treatment in placenta previa are contraindicated if bleeding is persistent even though small in amount at any one time, if the mother has a rare type of blood, or if hospital facilities are inadequate. In contrast to expectant treatment for placenta previa, temporizing with abruptio is contraindicated. Proper therapy for all women with antenatal hemorrhage in the last weeks of pregnancy include: hospitalization of the patient, initial control of shock, and sufficient blood and assistance to give adequate care. We believe it important to differentiate, whenever possible, placenta previa from abruptio placentae and the extent of the previa before treatment is given, because the prognosis frequently is different with the two complications for both mother and baby.

In this study one-sixth of the babies born by section of toxemic mothers were lost. Treatment of this disease is controversial. We subscribe neither to abdominal nor to vaginal delivery for all. Instead, the toxic state of the mother, the condition of the cervix, and the size of the baby and his chances for survival are considered in arriving at a method of treatment. Bed rest, isolation, restriction of sodium intake, and the administration of sedation with observation for at least 24 to 48 hours are advisable before interruption of pregnancy is considered. An unprepared cervix with little dilatation is not a contraindication to premature artificial rupture of the membranes with medical induction and does not constitute indication in itself for abdominal delivery.

Elective hysterotomy a week or so before the expectation date appears advisable after a previous section.

It was impossible to make accurate correlation between type of anesthesia used, time of clamping the cord after birth of the baby, methods of resuscitation, and fetal salvage. On the other hand, experience of others led us to believe that anoxia played a part in some of the fetal deaths. Inhalation anesthesia was used almost exclusively; regional anesthesia was seldom employed. The umbilical cord was usually clamped immediately after the baby was extracted. Landau and associates[3] have shown that immediate clamping of the cord may occasionally deprive a term baby of enough cord blood to give rise to shock and eventual death.

Surgeons in Knoxville not uncommonly delegated resuscitation of the newborn to someone who knew little or nothing about the procedure. Up until eighteen months ago two hospitals in this city did not possess a tracheal catheter in the operating room for resuscitation of infants.

The staff of hospital "A" has supported a monthly mortality conference for several years. Its fetal and maternal mortalities have been among the lowest recorded for a community of its size. This same institution had the lowest incidence of section in the study, lowest incidence of prematurity, and obstetric problems were handled in a manner outlined in the discussion. This experience recommends itself.

Finally, we recommend application of LeVake's[5] questions before doing a cesarean section:

1. Is proper consultation obtained and indication properly listed?
2. If indication is disproportion, is pelvic x-ray mensuration made?
3. What is the status of the fetus and the degree of maturity?
4. What are the duration of labor and condition of the membranes?
5. Have attempts at vaginal delivery been made previously?
6. Is there infection?
7. Is the woman cross-matched for blood transfusion?
8. If indication is eclampsia or abruptio placentae, why is section used?
9. What are the reasons for the type of anesthetic used?
10. If bleeding is the indication, what is the location of the placenta?

Summary and Conclusions

A study of 763 consecutive cesarean sections done in six nonteaching hospitals serving Knoxville, Oak Ridge, and Maryville, Tenn., showed the average fetal loss with abdominal delivery to be three times as great as the loss for all deliveries. Forty out of 88 fetal deaths occurred with inappropriate or poorly timed application of abdominal hysterotomy. Fifty out of 81 babies lost, and of known size, were premature. Experience in one hospital studied indicated periodic review of obstetric problems and complete study of the obstetric patient, including the fetus, by competent authority are desirable procedures to improve obstetric care in hospitals.

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Discussion

DR. ROBERT J. HAWKINS, Chicago, Ill.—The most basic revelation is the desperate need for hospital and departmental organization in all but one of the hospitals listed. It is to be regretted that the principles of correct obstetric procedures can be lost because a medical attendant is mentally lethargic, not interested, or exercises poor judgment. Equally at fault is the head of a department who knows what should be done but hesitates to enforce accepted procedures because he does not wish to question the judgment of his medical colleague. Such a department head is a liability to the hospital and should be replaced. When the standards of medical practice are lowered there are four groups injured. First and foremost the patient, who is not in a position to defend her rights, but places her trust in her physician; second, the hospital; third, the physician; and fourth, medicine as a whole.

In every well-run maternity unit in any hospital, big or small, charity or private, you usually find a department head who is deeply interested in this branch of medicine, who knows current trends in the field, guards well the standards of practice, and controls the department in his institution. He usually surrounds himself with a group of interested physicians who hold frequent departmental meetings where the work of the department is reviewed and a man must be prepared to defend his reasons for operative interference or procrastination. It is significant that in such institutions the members of the group get along well and are proud of their departmental achievements.

Dr. Diddle does not point with pride to the standards of obstetric practice in his community. He informed you that over two-thirds of the hospitals caring for 12,000 plus deliveries, responsible for 660 cesarean sections, had inadequate consultation in 95 per cent of the cases. He is not happy to report that of the 88 cases in which fetal deaths occurred, the indications were well taken in only 21, from the standpoint both of section and of preventability of the fetal death.

He points out that in over 75 per cent of these deaths the cesarean section was not indicated or was poorly timed. He further adds that in 5.5 per cent of the repeat sections the patient had a ruptured uterus.

The authors state that the diagnosis was not well established in some of the 52 cases of placenta previa, with 11 deaths, and the 38 cases of abruptio placentae, with 19 deaths, and they feel the cesarean section was not indicated in many of the cases of abruptio. The conservative, intelligent approach to placenta previa will salvage many infants and conservative vaginal delivery in cases of abruptio placentae will remove this fetal loss from the cesarean group and prevent the mother from becoming an obstetrical cripple. In these two respects we readily agree with the author. I believe Dr. Diddle minimized the influence, that anesthia plays in fetal deaths. We realize that many of these infants were dead at the time of the operation. The cause of death in 69 of 88 cases was prematurity or anoxia. The use of regional anesthesia will be an important factor in the salvage of the premature infant.

In considering induction of labor the statement is made, "An unprepared cervix with little dilatation is not a contraindication to artifical rupture of the membranes." The cervix still remains the barometer of the uterus, and to rupture membranes in an unprepared cervix is to add a further complication to an already complicated pregnancy.

Dr. Diddle and his associates have spent a tremendous amount of time collecting factual data, critically reviewing and analyzing them. They have been courageous enough to present them to this society because they feel other communities are not unlike their own. With the presentation of this paper the work of the authors is not finished. I hope that they will be encouraged to continue this undertaking and that the county medical association will endorse their study. It is only by the persistent, patient, and persevering efforts of men such as Drs. Diddle, Jenkins, Davis, and O'Connor that maternal welfare programs are instituted in communities. I am certain that when these data are presented to the doctors of this community they will recognize the need and support a maternal welfare program. I wish Dr. Diddle and his associates success in their efforts.

DR. HAROLD C. MACK, Detroit, Mich.—For a number of years, aided by Dr. G. M. Byington of the Detroit Department of Health, we have made a study of all cesarean sections performed in this metropolitan area. In the last four years we have accumulated data on 6,065 abdominal deliveries in which the maternal mortality declined steadily to reach a new low of 0.43 per cent in 1950. While it is gratifying to see the steadily decreasing maternal risk for cesarean section, it is disconcerting to observe that the prospect for survival of the infant has not improved as dramatically.

CESAREAN SECTIONS IN DETROIT, 1947 TO 1950

YEARS	TOTAL CESAREANS	MATERNAL DEATHS PER 1,000 CESAREAN SECTIONS	INFANT DEATHS PER 1,000 CESAREAN SECTIONS
1947	1,386	8.7	65
1948	1,474	6.1	70
1949	1,592	4.4	63
1950	1,613	4.3	62
Total	6,065		Average 65 per 1,000 cesarean sections

In 6,065 cesarean births during the past four years the infant death rate averaged 65 per 1,000 abdominal deliveries—a mortality rate more than twice as large as that for all infants who survived one month after delivery by all methods during this period. When it became obvious that the largest percentage of infant deaths followed cesarean section for antenatal hemorrhage (placenta previa and abruptio placentae) we began a separate study of infant deaths in repeat cesarean sections. We attempted to evaluate the fetal risk in the elective repeat section on the premise that here the timing of the operation and the condition of the mother could in most instances approximate the ideal. In such elective procedures, theoretically, no great risk should be imposed upon the fetus by a poor maternal state and there should be a minimum of hurried efforts to perform a lifesaving operation under poor surgical auspices.

REPEAT CESAREAN SECTIONS, 1947 TO 1950

YEARS	NUMBER REPEAT SECTIONS	INFANT DEATHS	INFANT DEATHS PER 1,000 CESAREAN SECTIONS
1947	248	13	52
1948	388	12	30
1949	416	10	24
1950	465	12	26
Total	1,517	47	3.09 (Average)

In 1,517 elective repeat sections performed in Detroit hospitals during this same period there were 47 dead infants—a mortality of 31 per 1,000 elective cesarean births. This figure is substantially greater than the average over-all infant death rate during the first month (23.2 per 1,000 live births) for the entire city during this period.

In an analysis of the causes of infant deaths after repeat sections the usual factors are encountered. Abnormalities incompatible with life are of course still present and unavoidable. Evidence of faulty judgment in timing the operation and in estimating the size and development of the infant are shown in the delivery of nonviable premature infants. Most striking, however, are the deaths ascribed to atelectasis. Fifteen, or almost one-third of the 47 infants, failed to establish normal respiration. It is noteworthy that all methods of anesthesia (local, spinal, caudal, as well as inhalation anesthia) were followed by this complication in the infant.

It would appear, then, that while cesarean section may well offer the baby a better chance than a difficult forceps operation or a vaginal birth after a devastating antepartum hemorrhage, abdominal delivery still does not guarantee a living child even under ideal conditions. It seems evident that there are some intangible factors in surgical delivery

through the abdomen which must still be overcome before we can accept cesarean section as the safest method of delivery as has been claimed in some quarters. This fact must be borne in mind when we observe the steady increase in the incidence of cesarean section for purely fetal indications.

DR. DIDDLE (Closing).—Dr. Hawkins asked how many sections were of the low cervical or classical type. The authors of this study were surprised to find that, of over 100 physicians doing cesarean section or helping with it, only 7 did the lower cervical attack; the majority used the classical attack.

It has been pointed out that of 213 patients who had repeated section twelve had incomplete or complete uterine rupture.

Since this study began, two hospital staffs initiated efforts to improve their fetal salvage. With the permission of Dr. S. Lambeth of Maryvill, Tenn., figures are given from one hospital. In the last 120 sections, by careful case analysis and selection of patients to be sectioned, the fetal loss was lowered from 9 to 5 per cent. This is a small number statisically but the trend is in the right direction.

In another hospital where an average of five to six cesarean sections are done per month, there has been no fetal loss this year.

STUDIES ON AUTONOMIC BLOCKADE. VI. THE MECHANISMS REGULATING THE HEMODYNAMIC CHANGES IN THE PREGNANT WOMAN AND THEIR RELATION TO THE HYPERTENSION OF TOXEMIA OF PREGNANCY*†

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AMONG the many striking physiologic changes which occur during pregnancy none are more fascinating than those which affect the circulation. In fact, during the last decade our knowledge has been markedly enriched by many enlightening contributions concerning the changes in blood volume, cardiac output, peripheral circulation, arterial and venous pressures, and other aspects of hemodynamics.[7-12] Although much progress has been made, many unknown and obscure questions still remain to be answered.

One of the most challenging problems dealing with circulation is the behavior of the blood pressure during normal and abnormal pregnancies. Several investigators have accumulated a large number of observations on the variation of arterial blood pressure readings throughout the course of gestation.[13-15] Although some agreement has been reached regarding qualitative patterns, nothing has been known concerning the cause of such changes. Hence, a confusion has resulted concerning the high limit which should be considered as a border line between the blood pressure of normal pregnancy and of toxemia of pregnancy. Since elevation of the arterial blood pressure is still considered by many authors as one of the most constant signs in the diagnosis of toxemia of pregnancy, a study which helps in elucidating the mechanism of the transitional changes between normal and abnormal blood pressure would be of some interest.

Of the various factors responsible for the maintenance of blood pressure in health and disease, none is more important than the peripheral resistance. Changes in the peripheral resistance are brought about by modifications of the caliber of the arteriolar system which has also been called with some justification the "stopcock of the circulation." Constriction or relaxation of this system would result in a respective rise or fall in the systemic arterial blood pressure.

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The venous system, also, by its effect on the cardiac output, participates indirectly in the regulation of the arterial blood pressure. If stagnation of a large amount of blood in the venous side of the circulation occurs, the venous return to the right heart, the right auricular filling and the "effective" circulating blood volume are impaired. This usually leads to a reduction in the cardiac output and consequently a fall in the systemic pressure.

It has been recently demonstrated that both arteriolar and venous systems are under the influence of vasoconstrictor impulses emanating from the autonomic nervous system.[16] The presence of vasodilator fibers has been a disputed subject and needs not be discussed here. Humoral agents also share in the regulation of both arteriolar and venous tone. To these two factors a secondary one should be added, an intrinsic factor inherent in the arteriolar walls but lacking in the veins. From the balanced interplay of neurogenic and humoral factors results a normally maintained blood pressure.

The discovery during the last few years of new drugs capable of blocking the neurogenic vasoconstrictor impulses and/or of counteracting some of the circulating humoral agents has made possible the evaluation of the factors involved in the maintenance of normal and abnormal blood pressure. In 1947 we initiated in this department a study of this kind aimed at understanding the mechanisms which regulate the blood pressure in normal nonpregnant women, normal pregnant subjects, and patients with various forms of hypertensive diseases of pregnancy, using several autonomic and adrenergic blocking agents, particularly tetraethylammonium chloride (TEAC). It is our impression that the data which have been accumulated during this time are sufficient to permit the evaluation of some of the factors involved in the diagnosis of the circulatory changes in normal and toxemic pregnancies.

Material

Table I shows the various series of cases which compose the present report. In it are also listed the year, the number and quality of patients studied, and the number of TEAC tests performed. Altogether, 191 subjects were studied between 1947 and 1951 with a total of 758 TEAC tests. Of the total number of patients, approximately one-half presented some form of hypertension; in the majority it was associated with pre-eclampsia. The criteria adopted for making the diagnosis of pre-eclampsia were described elsewhere[1] and need not be repeated here. Five series have been already published and for more detail the reader is referred to the original articles.[1-5] The sixth series consists of two parts:

a. Twenty-nine patients in whom an elevation of the blood pressure with or without edema and albuminuria was noticed in the last trimester of pregnancy and a definite diagnosis of pre-eclampsia was difficult to establish. These patients received several TEAC tests as a diagnostic aid in the prepartum and postpartum periods.

b. Twenty patients were subjected to TEAC testing every one or two weeks throughout their entire gestation and the puerperium. This was done in order to derive some information as to the time relationship of the hemodynamic changes during normal and toxemic pregnancies.

The seventh series comprises five normotensive pregnant subjects who were given desoxycorticosterone acetate (DOCA) and were simultaneously

tested with TEAC for several days. This was performed in an attempt to reproduce in normal pregnancy the response to TEAC observed in toxemia of pregnancy. This series will be the object of another report.[6]

In the present paper, these 7 series were pooled together and classified according to the condition of the patient when tested and the final diagnosis. In this way, it was expected that the results could be of some statistical significance.

TABLE I

SERIES NO.	SERIES YEAR	TOTAL CASES	NORMOTENSIVE NONPREGNANT	NORMAL PREGNANCY	PREECLAMPSIA	ECLAMPSIA	PREECLAMPSIA SUPERIMPOSED ESSENTIAL HYPERTENSION	ESSENTIAL HYPERTENSION	TOTAL TEAC TESTS
1	1948[1]	48	10	10	12	5	6	5*	180
2	1949[2]	14	--	5	5	--	--	4	35
3	1950[3]	22	--	10	10	2	--	--	60
4	1950[4]	32	5	12	11	2	2	--	73
5	1950[5]	21	--	17	--	--	--	4	28
6a)	Misc.	29	--	10	10	--	4	5	69
b)	Present	20	--	14	6	--	--	--	267
7	DOCA[6]	5	--	5	--	--	--	--	46
	Total	191	15	83	54	9	12	18	758

*Not published in that report.

Method

The method followed for testing the patient with TEAC has been the same since 1947 and it was fully described in other publications.[1, 2] In its essence, it consists of giving a single intravenous injection of 400 mg. (4 c.c.) of the drug after a resting control blood pressure had been recorded. After the injection, the blood pressure is taken every half-minute for about 10 minutes. Various points, however, should be stressed which would influence the accuracy of the test:

a. The patient should have a period of rest in bed or on the table for at least half an hour before the drug is given. This period is aimed to give a fairly stable control blood pressure.

b. During this control period, the blood pressure should be taken in the horizontal position every 5 minutes and for the last 10-minute period every minute. The control blood pressure, then, would be the arithmetic mean of all these readings.

c. The blood pressure should be taken always by the same observer in order to minimize errors from personal variations.

d. The same amount of the drug should always be given and the rate of injection should be the same. This rate should not exceed 20 seconds.

e. After the injection, the blood pressure should be recorded every half-minute during the first 10 minutes and every minute for another 5-minute period.

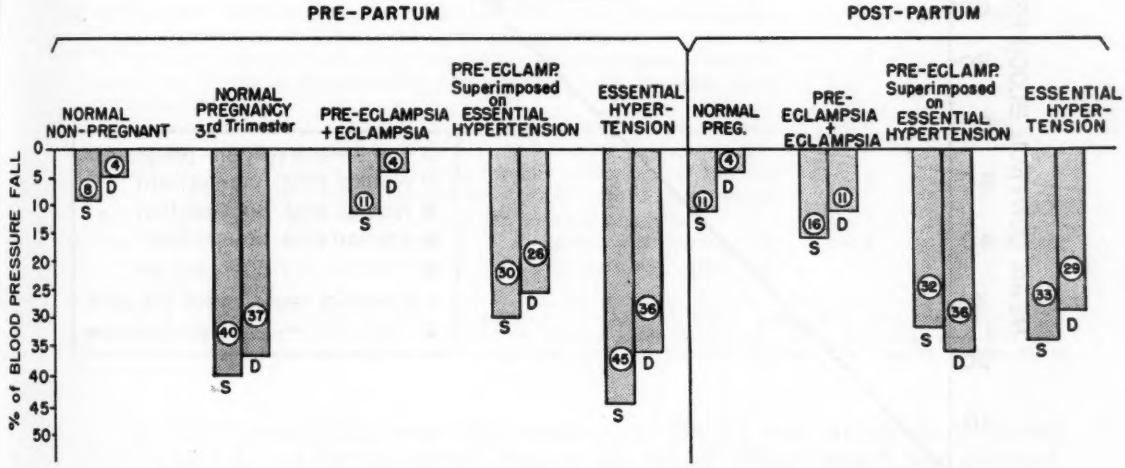
f. The patient should remain in the supine position for approximately 30 minutes after the test has ended. She should be instructed about the transitory postural hypotension and blurring of vision produced by the drug.

g. The TEAC "floor" is arbitrarily taken as the lowest point to which the blood pressure has descended within the first 10 minutes following the injection of the drug.

Since 1947 we have adopted the criterion of giving more value to the changes in the diastolic blood pressure because it reflects the status of the peripheral resistance. Thus, in a supposedly pre-eclamptic case, if the TEAC diastolic "floor" does not fall below 90 mm. Hg, this response is considered as suggestive of toxemia of pregnancy.

Results

1. Blood Pressure Changes in the Various Groups.—The results in the 191 cases are shown in Figs. 1 and 2. It can be seen that the normal nonpregnant group had a mean fall of 8 per cent in the systolic and 4 per cent in the diastolic blood pressure. In contrast, the normotensive pregnant group who were studied in the last trimester of pregnancy had 40 per cent of fall in the systolic and 37 per cent in the diastolic blood pressure. The pre-eclamptic and eclamptic patients were grouped together because there was little difference in their response. This group had a mean fall of 11 per cent in the systolic and 4 per cent in the diastolic blood pressure. When pre-eclampsia was superimposed on essential hypertension the mean fall was 30 per cent in the systolic and 26 per cent in the diastolic blood pressure. The group who had essential hypertension associated with pregnancy had 45/36 per cent of fall in the blood pressure.



MEAN RESPONSE TO TEAC IN 191 PATIENTS IN THE PRE-PARTUM AND POST-PARTUM PERIODS

Fig. 1.—The mean response to TEAC is expressed here as percentage of fall from the mean control blood pressure. All the means represent the arithmetic means of the patients studied. S = systolic, D = diastolic. The figures in the circles represent the exact percentage of blood pressure fall in each group. Note the striking difference between the response of normal pregnancy and pre-eclampsia and eclampsia in the prepartum period. In the postpartum period both groups had similar fall which was comparable to that of the nonpregnant subjects. The patients with pre-eclampsia superimposed on essential hypertension had more hypotension in the postpartum period which indicates that the presence of superimposed pre-eclampsia may prevent a larger fall in the blood pressure. There was no change from the prepartum figures in the response of patients with essential hypertension.

In the postpartum period, the most striking changes were observed in the normal pregnant group whose blood pressure in response to TEAC returned to the nonpregnant levels. The postpartum response of the toxemic group also showed similar changes. There was an insignificant difference from the prepartum figures in the patients who had essential hypertension. This was to be expected since the hypertension remained approximately the same after delivery.

Fig. 2 shows the mean blood pressure "floor" after TEAC plotted against the mean control blood pressure in the various series studied. It can be seen that the normotensive pregnant series grouped themselves together to the left of the curve and shifted toward the line following the delivery. The toxemic series were located in the upper part of the graph and descended toward the normotensive nonpregnant group following the delivery. The essential hypertensive cases showed inconsistent patterns.

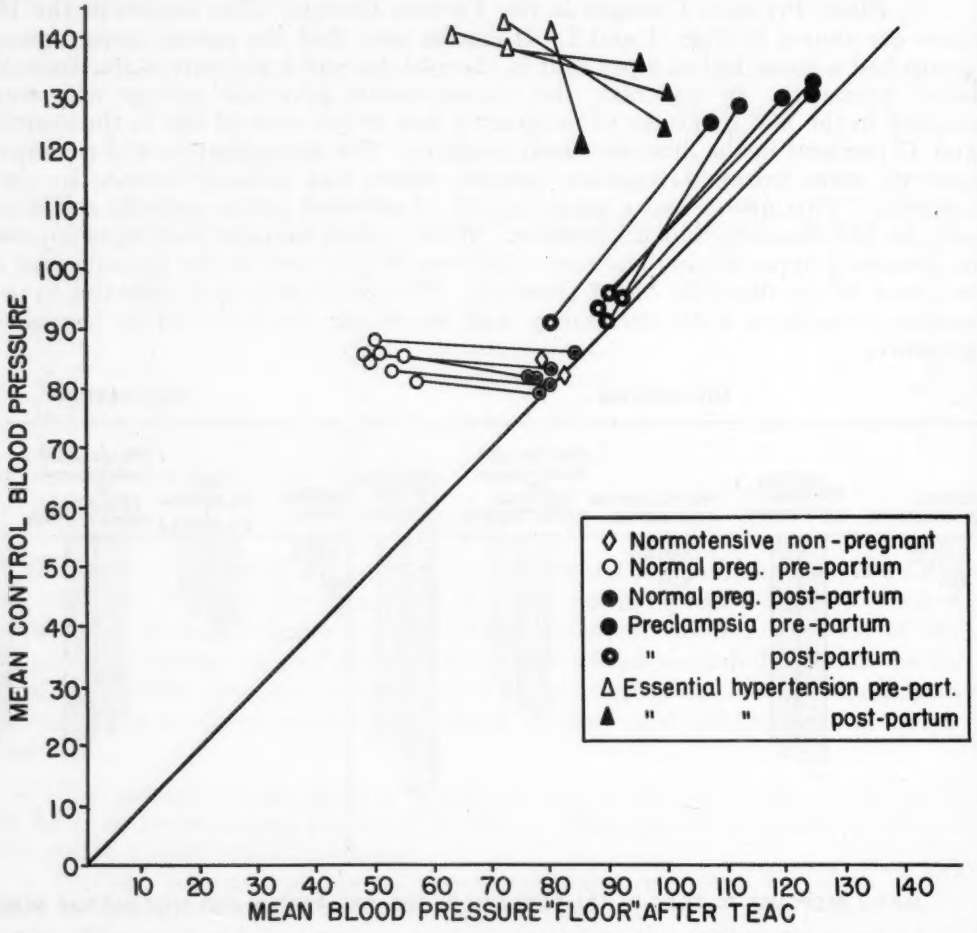


Fig. 2.—The mean blood pressure fall after TEAC ("floor") is plotted against the mean control blood pressure. In this figure, the mean was calculated according to the formula: $M = D + \frac{1}{3}(S-D)$, where M = mean, S = systolic, and D = diastolic. The cases in the normotensive nonpregnant series are close to the line. The normal pregnancies, pre partum, are to the left and shift toward the line in the postpartum period. The pre-eclamptic groups are in the upper left and descend toward the normotensive nonpregnant groups in the post-partum periods. The essential hypertensives remain scattered to the left of the line.

Table II shows the statistical analysis of the data on the 758 TEAC tests. It is evident from this table that a very significant difference exists between the response of the toxemic and the normal pregnant groups. Also, the statistical difference between the response of essential hypertensive and toxemic patients is very significant. The difference between pure pre-eclampsia and pre-eclampsia superimposed on essential hypertension is significant.

2. Changes in TEAC Response During Pregnancy.—Figs. 3, 4, and 5 show the progressive changes in response to the autonomic blockade with TEAC throughout the course of gestation. The earliest pregnancy studied in this

series of 20 cases was 13 weeks. It can be seen that in normal pregnancy the TEAC "floor" begins to fall around 18 or 20 weeks' gestation and follows a downward trend until the end of pregnancy. This pattern was observed in 14 cases out of the 20 which were studied during gestation and the response in the last trimester was similar to that seen in the other series of normal pregnancy. All of the 14 patients had normal pregnancy and delivery and the postpartum response was similar to that previously described for this type of patient.

TABLE II. STATISTICAL ANALYSIS OF THE DATA*

	T-SCORE	CRITICAL T-SCORE
1. Difference between normal pregnancy (3rd trimester) and normal nonpregnant—*Very Significant* = 1 per cent level of significance	11.2	2.8
2. Difference between normal pregnancy (3rd trimester) and pre-eclampsia and eclampsia—*Very Significant* = 1 per cent level of significance	10.4	2.8
3. Difference between normal pregnancy (3rd trimester) and essential hypertension—*Not Significant*	0.3	2.1
4. Difference between normal pregnancy (3rd trimester) and pre-eclampsia superimposed on essential hypertension—*Significant* = 5 per cent level of significance	3.2	2.2
5. Difference between pre-eclampsia and essential hypertension—*Very Significant* = 1 per cent level of significance	9.0	2.8
6. Difference between pre-eclampsia and pre-eclampsia superimposed on essential hypertension—*Significant* = 5 per cent level of significance	4.0	2.1
7. Difference between essential hypertension and normal nonpregnant—*Very Significant* = 1 per cent level of significance	9.8	2.8
8. *Insignificant difference* was found in the postpartum periods between pre-eclampsia and normal pregnancy and between essential hypertension with or without superimposed toxemia	0.4	2.3
9. *Significant difference* was found in the postpartum periods between the essential hypertension and the normal and pre-eclamptic groups	4.2	2.8

*The statistical analysis was performed on the 758 tests using the T-Score method as outlined in Lindquist *Statistical Analysis in Educational Research.* One per cent and five per cent levels mean there is one per cent and five per cent possibility that the results might have been due to chance.

In the 6 remaining cases the response to TEAC was strikingly different (Figs. 4 and 5). After an initial drop in the TEAC "floor" which was approximately parallel to that of the normal group, the TEAC "floor" began to rise, so at the last trimester of pregnancy the "floor" was very similar to those found in toxemia of pregnancy. All of the 6 patients developed definite signs of toxemia during the last trimester of pregnancy and in 2 of these, toxic separation of the placenta occurred. The most interesting finding in these cases was that the TEAC "floor" began to ascend even before any excessive weight gain, hypertension, or albuminuria was noted. When these symptoms later became evident, the rise in the TEAC "floor" was more prominent.

3. TEAC Test Given as Aid in the Diagnosis of Toxemia.—Of the 29 cases in which TEAC tests were used as an aid in the diagnosis of toxemia of pregnancy, 10 cases showed response to TEAC similar to that of the normal pregnant groups. The follow-up of these cases confirmed the absence of toxemia. Ten patients became later frankly toxemic; in 7, the TEAC "floor" was high and very similar to that of the toxemic group. Also the TEAC test was of help in differentiating 4 cases with essential hypertension underlying the toxemia and in which blood pressure fell markedly with the test. A postpartum follow-up of these patients confirmed the diagnosis of pre-existing hypertension.

4. Side Effects.—No serious ill effect which could be attributed to TEAC was encountered in any of the series studied. The administration of the drug was frequently attended by tachycardia, tingling, metallic taste, and sensation of warmth. All of these symptoms disappeared within 2 minutes' time. Severe

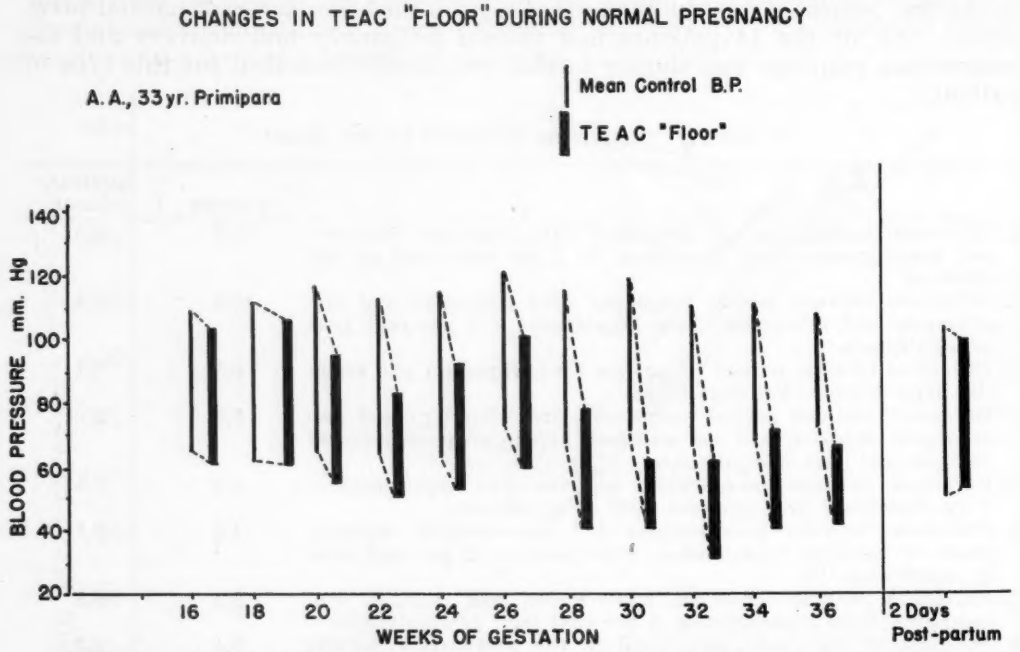


Fig. 3.—Biweekly TEAC tests in a patient followed throughout her gestation. The TEAC "floor" (thick line) begun to descend around the twentieth week and followed a downward course until the time of delivery. In the postpartum period, the response was similar to that of nonpregnant subjects.

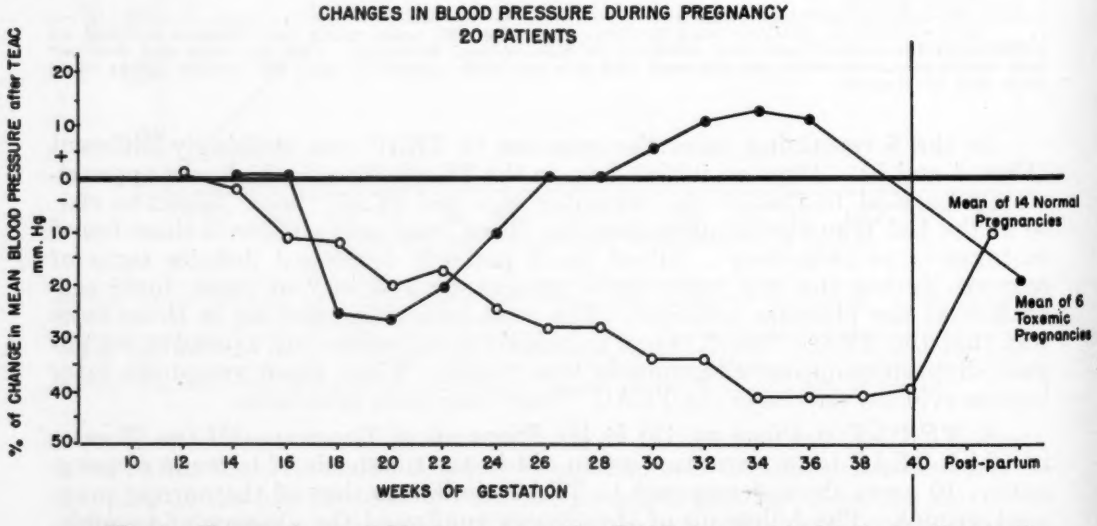


Fig. 4.—Changes in mean blood pressure after TEAC (mean calculated according to the formula in Fig. 2) throughout the course of gestation in 20 patients. The figures above the zero line represent lack of fall after the test. Those below the line represent the percentage of fall from the control pressure. It can be seen that the 14 patients who ended with normal pregnancy and delivery had a progressive fall in the blood pressure with the progress of the gestation. The other 6 who developed toxemia of pregnancy showed a fall in the blood pressure up to the twentieth week of gestation, but then a progressive rise, so at the end of gestation the response to TEAC was frankly equal to that of pre-eclamptic patients. Note the opposite shift in the postpartum periods.

hypotension with signs of shock may be seen occasionally in normotensive pregnant subjects but these conditions can be corrected immediately by raising the legs 90 degrees.

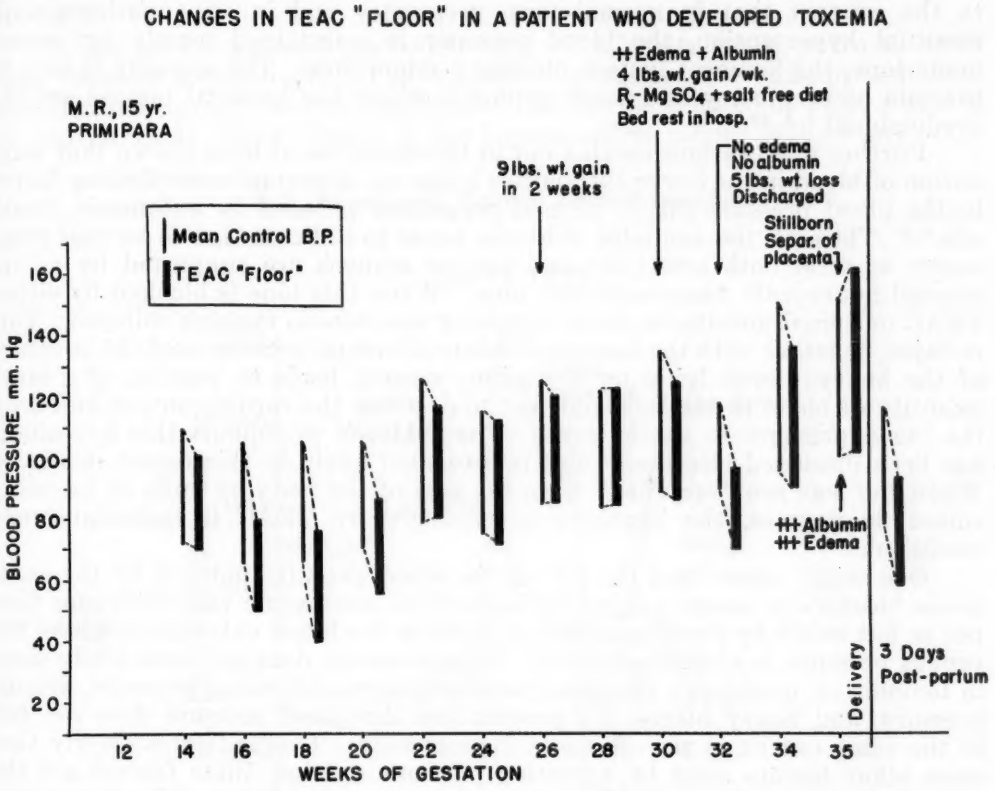


Fig. 5.—Biweekly TEAC tests in a patient followed during the entire gestation and who later developed pre-eclampsia and toxic separation of the placenta. Note the initial low TEAC "floors" and the progressive rise even before any weight gain was evident. At 30 weeks, the patient was admitted to the hospital with frank toxemia of pregnancy. After 2 weeks of treatment she improved markedly. The TEAC "floor" became low. At 34 weeks she was admitted, this time with separation of the placenta, hypertension, edema, and albuminuria. Note the strikingly high TEAC "floor" at this time and the low one following delivery.

Comment

Acheson and Moe[17] and others[18-20] have demonstrated in man and animal that the tetraethylammonium ion acts by blocking the autonomic nervous system at the ganglionic level. The blockade involves both the sympathetic and parasympathetic pathways. The drug does not inhibit the action of epinephrine. Clinically, this agent has proved to be an excellent physiologic tool in the evaluation of the neurogenic factors which contribute to the maintenance of blood pressure in health and disease.[19, 20] It has been shown that an intravenous dose of 400 mg. is sufficient to produce a fairly complete blockade of the autonomic vasoconstrictor impulses to both arteriolar and venous systems.[4, 5, 21] After this blockade is achieved, the blood pressure level which remains is supposed to be supported by humoral mechanisms together with the intrinsic tone of the arteriolar walls.

Previous works have shown that normal pregnancy at term responds with a dramatic fall in blood pressure to autonomic blockade with either TEAC or spinal anesthesia.[1-5] The same response is observed in patients with essential

hypertension, particularly in those cases where there is a predominant neurogenic tone. On the contrary, the blood pressure of patients with toxemia of pregnancy or with acute glomerulonephritis shows a negligible response to the blocking action of TEAC and spinal anesthesia.[1-5, 20] These observations led to the concept that in normal term pregnancy and in some patients with essential hypertension, the blood pressure is maintained mostly by neurogenic tone, the humoral factors playing a minor role. The opposite is seen in toxemia of pregnancy and acute nephritis where the humoral factors are the predominant.[4, 5, 20]

Further observations carried out in this department have shown that stagnation of blood in the lower extremities is also an important contributing factor in the blood pressure fall of normal pregnancy induced by autonomic blockade.[4, 5] Thus, all the available evidence tends to indicate that in normal pregnancy at term both arteriolar and venous systems are supported by an increased neurogenic vasoconstrictor tone. When this tone is blocked by either TEAC or spinal anesthesia, both arteriolar and venous systems collapse. This collapse, together with the increased intra-abdominal pressure and the pressure of the heavy uterus lying on the major vessels, leads to pooling of a large quantity of blood in the legs sufficient to decrease the cardiac output and drop the blood pressure to shock levels. The evidence to support this hypothesis has been discussed elsewhere[5] and is presented again in this report in Fig. 6. When the legs are "excluded" from the rest of the body by cuffs or by being raised 90 degrees, the hypotension produced by TEAC is instantaneously abolished.

One might argue that the fall of the blood pressure induced by the autonomic blockade is caused not by the blockade of neurogenic vasoconstrictor tone per se but solely by the stagnation of blood in the lower extremities where the venous pressure is already elevated. This, however, does not seem likely since in toxemia of pregnancy the same increased intra-abdominal pressure, venous pressure, and heavy uterus are present but the blood pressure does not fall to the same extent as seen in normal pregnancy. This indicates clearly that some other factors must be operating. In our opinion, these factors are the excessive neurogenic tone in normal pregnancy and the humoral one in toxemia of pregnancy. This difference in the mechanisms which support the circulation in normal pregnancy and toxemia of pregnancy explains well why normal pregnant subjects faint easily when standing and why they are susceptible to the action of spinal anesthesia, whereas the toxemic patients are not. The negligible fall in the blood pressure of the latter group as demonstrated in the analysis of the response of a large group of patients indicates the absence of venous pooling and establishes beyond doubt the lesser activity of neurogenic tone in this disease.

As to the time of gestation during which these circulatory changes are most likely to occur, the present data seem to indicate that the shift from neurogenic tone characteristic of normal pregnancy to humoral control of toxemia occurs between the twentieth and twenty-fourth weeks of gestation. In the 6 patients who developed toxemia of pregnancy while they had been followed throughout the gestation, the rise in the TEAC "floor" began at 22 weeks and continued progressively until the delivery. Of considerable interest is the fact that the rise in the TEAC "floor" characteristic of toxemia of pregnancy seems to appear very early and can be lowered to levels equal to that of normal pregnancy by bed rest and other treatment (Fig. 5). This observation has been previously described[1] and is confirmed again in the present study. On the other hand, administration of salt or ACTH to normotensive pregnant subjects might invoke elevation of their TEAC "floor" to levels seen in toxemia of pregnancy.[22, 23] It could be contended that the variations in the response to

TEAC throughout the gestation is caused by the daily changes in humoral and neurogenic components of the blood pressure as has been described by Levinson and associates.[24] This seems very unlikely since the changes observed here were of much higher magnitude and followed a progressive course as illustrated in Fig. 4.

It has been suggested previously that TEAC tests might prove to be of some value as a diagnostic aid in toxemia of pregnancy.[1, 3] The present data give further support to this hypothesis. As can be seen from Figs. 4 and 5, the rise in TEAC "floor" began in the 6 cases before weight gain or any other

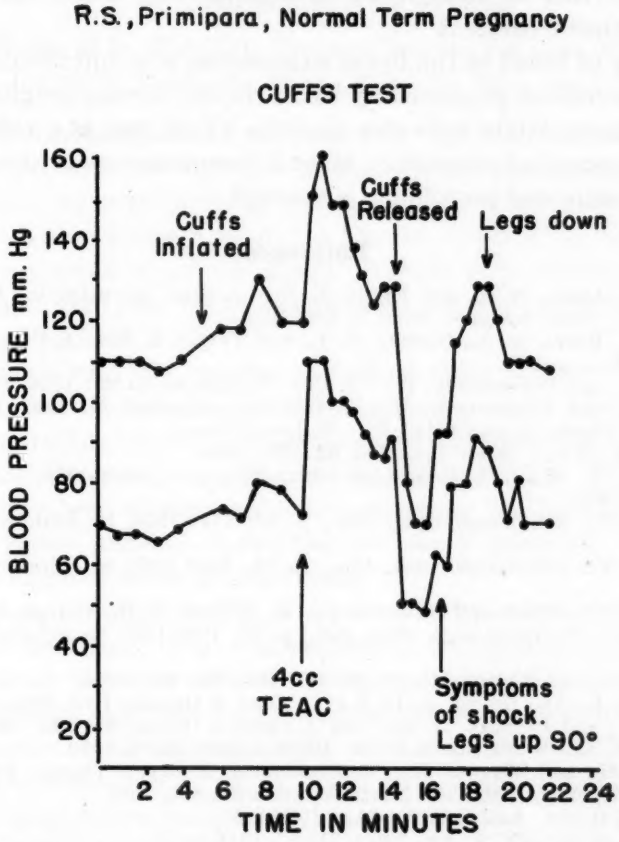


Fig. 6.—The venous pooling in the legs is illustrated in this figure. The legs were first "emptied" of blood by being "milked" and blood pressure cuffs were fitted around the proximal parts of the thighs. The cuffs were inflated to levels above the systolic pressure. TEAC did not produce any fall in the blood pressure until the cuffs were released. Immediately thereafter, the patient went to shock. This was instantaneously corrected by raising the legs 90 degrees.

sign of toxemia was evident. Furthermore, in the cases where the TEAC test was used as a diagnostic aid, it proved to be correct in approximately 75 per cent of the cases. In these patients, the diastolic "floor" remained always on or around 90 mm. Hg and was lowered only by treatment and bed rest. Furthermore, the results of the statistical analysis offer evidence of the validity of this test. The fact that the responses of the pre-eclamptic and eclamptic groups differ markedly from the rest except the normotensive nonpregnant group attests to the value of the TEAC test as a screening aid for the diagnosis of toxemia of pregnancy.

Summary and Conclusions

1. A statistical analysis of the results obtained in the study of 191 patients submitted to 758 TEAC tests is presented.

2. The data confirm previous hypothesis that the blood pressure of normal pregnancy is maintained by an excessive neurogenic tone, whereas that of toxemic pregnancy is supported by humoral mechanisms.

3. The shift from neurogenic to humoral support of the blood pressure occurs around the twentieth week of gestation. Thereafter, the response to TEAC characteristic of toxemia becomes more evident and can be modified by bed rest and other treatment.

4. Pooling of blood in the lower extremities is a contributing factor in the genesis of hypotension produced by TEAC in the normal pregnant woman.

5. The present study indicates that the TEAC test is a valuable aid in the diagnosis of toxemia of pregnancy, since it becomes more evident before weight gain, hypertension, and proteinuria are noted.

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CAUSES OF DEATH IN CARCINOMA OF THE CERVIX INFLUENCING MODERN TRENDS IN TREATMENT*

An Analysis of 248 Deaths From Charity Hospital of Louisiana at New Orleans

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PROMPTED by dissatisfaction with our own results in treatment of carcinoma of the uterine cervix as well as with the extreme variances of opinion in the profession today, we have reviewed the records of 248 patients with this disease who have died within a recent period at Charity Hospital in New Orleans. We believed that a correlation of the causes of death with various other factors in these cases might give us a better insight into the ways of prolonging the comfortable lives of patients.

In agreement with the reports of various other authors,[1-2] we found that death in carcinoma of the cervix is principally the result of uremia, infection, or hemorrhage, rather than of the carcinoma itself. Modern trends in therapy have given us the weapon of antibiotics against infection. Blood replacement and surgery have been of some value in prolonging the lives in cases of hemorrhage. This leaves ureteral obstruction to take a relatively increased toll as the immediate cause of death in this disease.

A great deal of thought today is concerned with whether radiological treatment, surgical treatment, or a combination of both should be used. The purpose of this paper is not to enter into this controversy but to present what we think is a practical approach to prolonging the lives of many of the patients who have uremia or hemorrhage. Our review shows that obstruction of the ureters was the immediate cause of death in a large proportion of the cases studied. We have drawn certain conclusions regarding treatment for cure and especially for prolonging comfortable life in these patients.

Material

No one surgeon or single group of surgeons can expect to have sufficient cases of their own to prove the efficacy of any procedure within a reasonable time. In the thirteen-year period, 1938 to 1950, inclusive, 248 patients with carcinoma of the cervix died at Charity Hospital. During this time, there were 1,247 separate admission diagnoses of carcinoma of the cervix. The present series is concerned, of course, with the 248 patients who were admitted to the hospital for terminal care; most of these had previously been treated at this institution. There were 84 white patients and 164 Negro, approximately one to two.

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The following tables contain various compilations of data taken from the case histories of these patients.

TABLE I. AGE AT TIME OF DEATH

AGE (YEARS)	URETERS OBSTRUCTED	NOT OBSTRUCTED
Up to 30	8	4
31-40	28	22
41-50	38	30
51-60	40	21
61-70	30	12
71	7	6
Unknown	0	2
Total	151	97

The age distribution (Table I) conforms to that which would be expected in deaths from this disease. A significant fact shown in this table is that older women with cervical carcinoma have a slightly greater tendency to die with obstructed ureters than do younger women. Fifty-one per cent of those who died with obstructed ureters were over 50 years old, while only 40 per cent of those without evidence of obstruction were over 50.

TABLE II. PARITY IN PATIENTS WHO DIED OF CARCINOMA OF CERVIX

PARITY	URETERS OBSTRUCTED	NOT OBSTRUCTED
0	24	18
i	24	23
ii	20	14
iii	13	5
iv	6	6
v	10	3
vi	4	2
vii	6	4
viii	5	4
ix	5	4
x-xvii	5	0
Unknown	29	14
Total	151	97

When the series is examined from the point of view of parity (Table II), we observe that this probably does not affect the occurrence of ureteral obstruction.

In Table III we see the final causes of death in this series with the percentage of patients who died from each cause.

TABLE III. PRIMARY CAUSES OF DEATH IN PATIENTS WITH CARCINOMA OF CERVIX

CAUSE OF DEATH	TOTAL CASES	PERCENTAGE	NO. AUTOPSIES
Uremia and pyelonephritis	128	51.6	38
Hemorrhage	34	13.7	8
Carcinomatosis and cachexia	28	11.3	9
Heart and circulatory complications	20	8.1	6
Intestinal obstruction	12	4.8	3
Peritonitis	8	3.2	4
Miscellaneous	18	7.3	2
Total	248	100.0	70

The small number of patients who died of peritonitis is worthy of note. These include postoperative and postirradiation patients and their being so much in the minority is a tribute to the effectiveness of chemotherapy and antibiotics.

Ureteral Obstruction

The literature reveals several studies of the prevalence of ureteral obstruction as related to the cause of death in carcinoma of the cervix. In 57 autopsies, Pearson[3] found stricture of the ureters in 75 per cent, with uremic deaths in 25 per cent. DeAlvarez[4] in 55 autopsies found ureteral obstruction in 40 per cent. Henriksen[5] found uremia the cause of death in 58.5 per cent of untreated and 49.3 per cent of treated cases. Herger and Schreiner[6] report 54 per cent ureteral obstructions, Aldridge[7] reports ureteral obstructions in 34 per cent of all cases of carcinoma of the cervix.

We see from Table III that 51.6 per cent of our patients died from uremia or pyelonephritis. In contrast to the practice of others, we have not attempted to separate these two conditions as causes of death in cases of ureteral obstruction. As the rising nitrogenous elements of the blood accompanied the fever and urinary findings in a great many of the cases, separation into "obstructed kidneys" and "infected kidneys" was frequently impossible. All of this group, however, showed definite evidence of ureteral obstruction either clinically or at postmortem and died what was believed to be a death from renal causes. In addition, there were 23 cases of ureteral obstruction in the total of 120 patients who died of causes other than uremia and pyelonephritis (Table IV), so that 60.9 per cent of our series had ureteral obstruction.

TABLE IV. URETERAL OBSTRUCTION IN PATIENTS WHO DIED OF CARCINOMA OF CERVIX

		NUMBER OF CASES	PERCENTAGE
Ureteral obstruction		151	60.9
Uremia and pyelonephritis	128		
Deaths from other causes	23		
Not obstructed		97	39.1

We had hoped in the beginning of this study to show statistically some method of predicting which patients were more likely to die from urinary obstruction. We were, however, unable to correlate any factors (with the possible exception of age) as favoring or hindering this complication of the disease. Parity, stage at which treatment was begun, symptoms, or pathological type did not affect the proportion of patients dying in uremia. By calculating the average length of time between onset of general symptoms or onset of signs of ureteral obstruction and death, we hoped to formulate conclusions on the significance of the time factor and determine whether early treatment was more likely to result in ureteral obstruction or in death from other causes. In patients in the latter stages (clinical Stages III and IV) at the time of diagnosis, little correlation proved to be possible. However, patients with earlier diagnoses (clinical Stages I and II), who ultimately succumbed to ureteral obstruction with uremia, lived longer than those who died not obstructed. Calculating the time from treatment to death in the earlier stages (Table V), 39 per cent died in less than one year and 61 per cent in more than one year when the death resulted from kidney obstruction. On the other hand, in cases diagnosed early with death from other causes, 56 per cent died in less than one year and 44 per cent in over a year. From these data we conclude that there may be sufficient time to alleviate this obstruction after appearance of early signs of its development.

TABLE V. SURVIVAL TIME IN CASES DIAGNOSED AT CLINICAL STAGES I AND II

	DIED FROM UREMIA AND/OR PYELONEPHRITIS	DIED WITHOUT OBSTRUCTION
Survived less than 12 months	39%	56%
Survived more than 12 months	61%	44%

Distant Metastases

That carcinoma of the cervix is not a disease generally resulting in distant metastases is well recognized. We owe a great deal to Henriksen[5] for his careful treatise on the local spread of this disease. Fig. 1 shows the spread to the primary group of lymph nodes and Fig. 2 the secondary spread. The autopsies in our series were not done specifically to trace out this progression of the disease but in general Henriksen's pattern of lymphatic extension was noted. He found distant metastases in 53 per cent of treated and 27 per cent of untreated cases, suggesting the probably arresting effect of irradiation on the local growth and involved nodes, resulting in longer survival and greater opportunity for development of metastases.

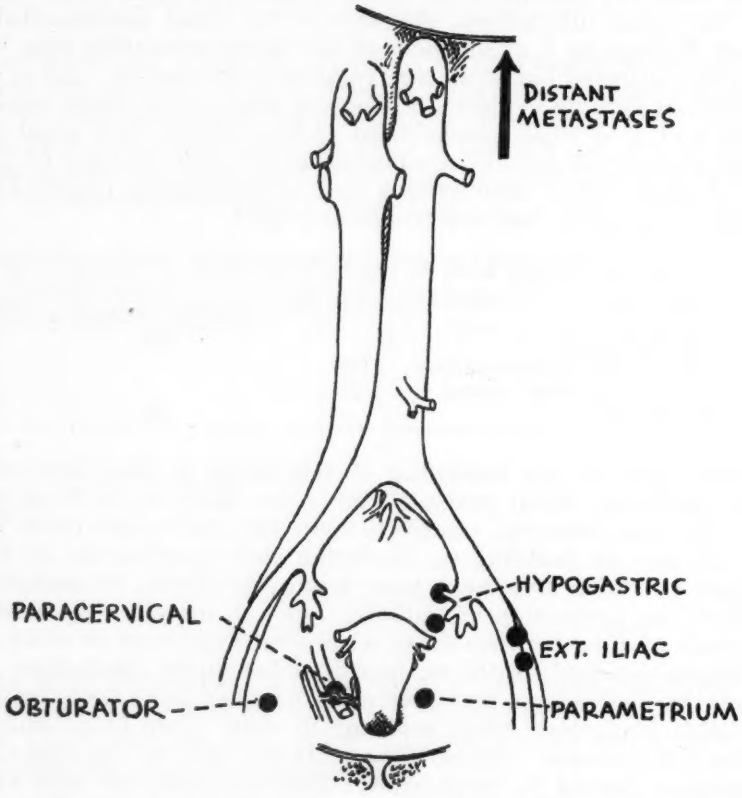

Fig. 1.—Primary group of lymph node metastases. (Adapted from Henriksen.[5])

In our 70 autopsy cases, we found distant metastases in 23, or 32.9 per cent. Distant metastases in the remaining 178 nonautopsied cases were diagnosed clinically in 29 cases, or 14.1 per cent. Apparently only about one-half

Table VI. Location of Distant Metastases

ORGAN	NO. OF INSTANCES
Lung	33
Liver	15
Bone	15
Peritoneum	12
Intestine	5
Brain	3

of the instances of distant metastases are detected by clinical methods alone. However, it is worthy of note that, except in patients who died of carcinomatosis, many of these metastatic foci lay quiescent and had little to do with the actual demise of the patient. The location of these distant metastases is shown in Table VI.

Irradiation Results

In the last decade, ureteral obstruction resulting from x-ray or radium treatment has been a rarity, undoubtedly because of the refinement in the technique of administering these agents. In the series under study, we did not see fulminating uremia shortly after irradiation. Neither did our autopsy findings show cases with only inflammatory swelling or late fibrosis following irradiation; but rather, the clinical findings were those of progressive obstruction following extension of the disease and this was, in turn, borne out at the autopsy table.

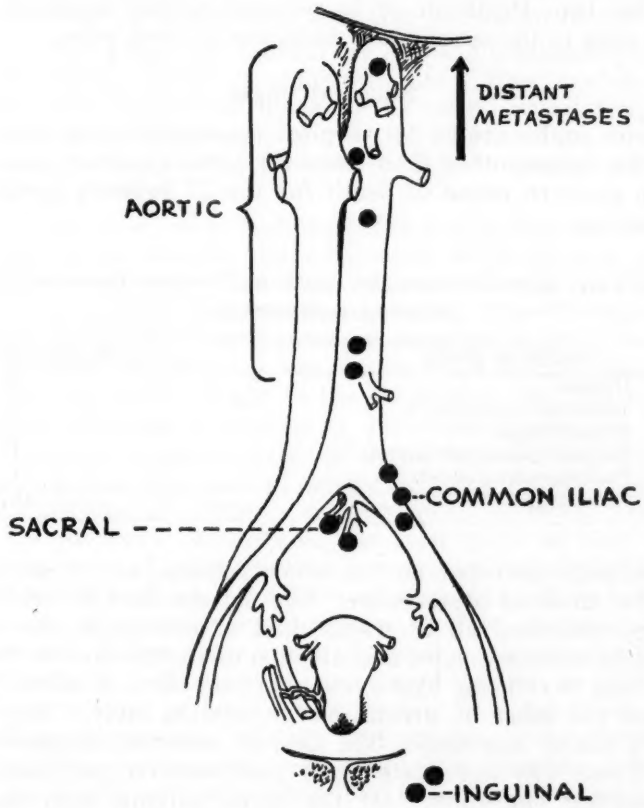

Fig. 2.—Secondary group of lymph node metastases. (Adapted from Henriksen.[5])

Hemorrhage

As has been previously stated, hemorrhage was considered the primary cause of death in 34 cases, or 13.7 per cent, of our series. There were many others in whom hemorrhage, though not the precipitating cause of death, was an important factor in the patient's debilitation and in increasing the ease with which some other cause resulted in death.

There were, in this series, a number of operative procedures the primary purpose of which was to control hemorrhage. The results from these procedures, however, were unsatisfactory. The primary treatment of hemorrhage in this

condition is blood replacement, at best a temporary lifesaving method, but a procedure which was of immeasurable value in the preparation of patients for extensive surgery. However, there is a limit in replacing blood in hopeless cervical cancer cases, after which one hesitates to put the family and friends through the drain of futile transfusions.

Pain

Pain relief in late carcinoma of the cervix shows little to gratify the physician or the patient. In reviewing these 248 records, we were impressed with the infrequence of pain relief as an important factor. Prefrontal lobotomies, caudal resections, Dolamine spinal injections, alcohol injections, and other procedures were used, often unsatisfactorily. However, in the actual handling of these patients, relief of intractable pain is frequently an important part of their care. In the final stages, simple dehydration supplementing the opiates as advocated by Jean Pratt[8] in an as yet unpublished paper on terminal care of the patient adds to the satisfactory handling of these cases.

Surgical Cases

In the series under study, 29 surgical operations were performed for the treatment of the disease other than those for hemorrhage or pain relief. Table VII shows the assigned cause of death for the 13 patients operated on for intestinal obstruction.

TABLE VII. ASSIGNED CAUSE OF DEATH OF PATIENTS OPERATED ON FOR INTESTINAL OBSTRUCTION

CAUSE OF DEATH	NUMBER OF CASES
Uremia	6
Intestinal obstruction	4
Hemorrhage	1
Noncarcinomatous uremia	1
Postoperative shock	1
Total	13

Among patients operated on for other reasons, one cystostomy was mistakenly done for ureteral obstruction. The patient died in uremia. Three patients had nephrostomies, all of whom died of uremia in one month or less. Five patients had ureterostomies and all died of uremia in less than one month. Two patients had Wertheim hysterectomies, one died of shock one day postoperatively and the other of uremia eleven months later. One had a radical Wertheim with gland resection. She died of noncarcinomatous uremia three years later. There was one death from postoperative peritonitis thirty days after a Brunschwig operation. Of the three patients who underwent total hysterectomy, one died of postoperative shock four days later (a ureter was cut at the time of surgery), the second died of pulmonary embolus two weeks later,

TABLE VIII. SURGICAL PROCEDURES

Relief of intestinal obstruction	13
Cystostomy	1
Nephrostomy	3
Ureterostomy	5
Wertheim	2
Wertheim plus gland resection	1
Brunschwig	1
Total hysterectomy	3

and the third died of cachexia two years later. Thus, we see discouraging results in ten cases in which relief of actual or potential ureteral blocks was attempted.

Comment

The uterus is surrounded by a vascular plexus of lymphatic structures, the main channels of which extend along the bases of the broad ligaments. Direct carcinomatous infiltration of surrounding tissues takes place along fascial planes through which there is usually only little early spread. In carcinoma of the cervix the paths of least resistance to invasion extend laterally into the parametrial regions along the ligament of Mackendrodt at the base of the broad ligament. The fascial planes anteriorly between the cervix and the bladder and posteriorly between cervix and rectum inhibit direct extension to these structures. Similarly, the fascial covering of the ureter prevents spread of the malignancy into the ureters but these nonrigid structures are easily compressed and kinked by extrinsic growths with resulting shutdown of the urinary flow.

We maintain that x-ray and radium are still the treatments of choice in all carcinomas of the cervix except carcinoma in situ. Here a wide hysterectomy may be in order. For those who desire it, the initial irradiation treatment in Stage I and early Stage II may well be followed by some type of wide hysterectomy and gland dissection. And here the treatment should rest in the hope that a cure has been obtained.

According to our data, when complete cure is not obtained as evidenced by an advanced stage of the disease, radioresistance, or recurrence, uremia will be the cause of death or ureteral obstruction will contribute to the debilitation and ultimate death in a significant proportion of cases. For the treatment of this type of case, some men are turning to extensive surgery.

The small number of intestinal obstruction cases which were seen (4.8 per cent of deaths in this series) leads to the conclusion that the removal of the rectum in a pelvic clean-out procedure is unnecessary when the rectal wall is not involved. However, transplantation of the ureters not only allows for better surgical principles in the treatment of cancer by block dissection of the involved area but also is the phase of extensive surgery which offers the greatest promise of prolonging the patient's comfortable life even when no cure is obtainable. In performing any type of pelvic clean-out, carcinomatous growth surrounding the ureters is sometimes found. We are sure that many of us have been guilty of cutting through cancerous tissue contrary to best surgical principles and leaving the ureters to follow their original course. We are of the opinion that ureteral transplantation in this type of case should be done, as obstruction would otherwise be almost certain to develop ultimately. Removal of the involved area en masse, avoiding, if possible, cutting through cancerous tissue is the only way to obtain sufficiently clean surgical results for effecting a cure. The decision must be made here as to whether to bring the ureters out through the skin or into the bowel. In the Charity Hospital series, another outlet to the urinary flow was made surgically in only ten cases, and, of necessity in our study none of these survived. In all of these cases, however, as in Aldridge's[7] series, the diversion of the urinary stream was too late to be of benefit.

In those patients who show a progression of disease, we hope that extensive surgery may give a cure in some few cases, or, more probably, give prolonged comfortable life. As blockage of the ureters is the most common outcome after failure to obtain a cure, this complication should be watched for most carefully. Repeated ureteral dilatation has been tried in the past and discarded. We believe that some routine of expectant diagnosis, such as bimonthly urinalyses, monthly pelvic examination and blood urea nitrogen determination, and quarterly cystoscopies may be of value in detecting evidence of early ureteral ob-

struction. When these signs appear, and not after a well-developed pyelonephritis exists, a decision to divert the urinary flow could be made. To the best of our knowledge, such a plan as this has not been reportedly tried. We propose it tentatively on the basis of the studies reported here.

There has been considerable discussion recently concerning the advisability of any extensive surgery in carcinoma of the cervix. Some shun this phase of the treatment because of their unfamiliarity with the surgical principles involved. There are, however, sufficient trained gynecologists with well-organized surgical teams so that technical skill or the physical stamina of the surgeon should not discourage further treatment where it is indicated.

The patient's psychological and emotional approach to surgery in a case of carcinoma of the cervix is an important part of the preoperative preparation. Of necessity it assumes the patient's knowledge of her condition. To persuade a comfortable, symptom-free patient to undergo an operation which will change her physiological functions is indeed difficult. The final decision should be in the hands of the patient and her family after the various surgical procedures and their possible outcomes have been carefully explained. A patient has the right to accept or reject a procedure which may remove the bladder and vagina and even leave her with a wet colostomy.

Regarding the small percentage of cases in which hemorrhage is a threat to life, we believe that a block dissection will eradicate the area of tissue in which hemorrhage is most likely to occur and thus prolong the comfortable life of the patient. The cause of death following such surgery has been reported for only a few cases. We believe that the majority of patients not succumbing to postoperative shock or hemorrhage will eventually die in uremia.

In conclusion, we have found that 65.3 per cent of the patients who die of carcinoma of the cervix are dying primarily from urinary obstruction or hemorrhage. Any hope for saving or prolonging the comfortable lives of these patients lies in relatively early surgery. Extensive early surgery designed for complete cure may be part of the answer. Urinary diversion alone is a partial answer in the cases where cure has failed. We would deem it a successful trend if, among patients who die of carcinoma of the cervix, we could increase the relative percentage of those who die of cachexia and carcinomatosis and proportionately lower the percentage of those who die from the local complications.

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Discussion

DR. MALCOLM B. DOCKERTY, Rochester, Minn.—Not once in a decade does an article appear detailing the necropsy findings in carcinoma of the cervix, and practically none of these studies has left us a legacy of ideas designed to improve the treatment of the terminal suffering brought about by this disease.

The essayists have disclosed how the *bêtes noires* of sepsis and hemorrhage have, in a measure, been erased from the picture, leaving us with an increasing number of patients who die from the effects of ureteral obstruction and pyelonephritis. The question they raise as a result of their investigations is a provocative one: "May not early diversion of the urinary stream contribute a measure of comfort and a lengthening of the twilight hours for patients whose cervical carcinomas have defeated attempts at eradication?"

By way of preparing my discussion I reviewed the necropsy data concerning some 86 patients who had died from the effects of carcinoma of the cervix uteri. The year 1938 gave me a convenient mid-point in that it provided a demarcation between 43 cases comprising an "old series" and 43 cases in a more recent group.

The mean duration of life from treatment to death was six months for patients of the old series and twelve months for those in the new series. This difference of six months of added life in the new series, as the essayists have pointed out, reflects improvement in management by means of radium and roentgen rays as well as better performance in combating hemorrhage and sepsis.

Hydroureter, hydronephrosis, and pyelonephritis contributed materially to the fatal outcome in 62 per cent of these 86 individuals. These complications were half again as common among patients in the new series as among those in the old series, the increasing incidence paralleling the increased duration of life. In all but 2 of these individuals hydronephrosis was on the basis of periureteral cuffing with malignant tissue. This was noted by the essayists, and it must be carefully taken into account in any operation designed to divert the urinary stream.

In our series, fistulas, either vesicovaginal, rectovaginal, or "combined," were encountered in 15 per cent of the cases. They were about twice as common in patients of the new series as in patients of the old, being in both almost always on a malignant basis. All will agree, I am sure, that surgical diversion of the urinary stream into the colon is to be preferred to its "malignant" diversion into the vagina. Drs. Sellers and Ward had this in mind when they referred to the urologic complications following Brunschwig and other pelvic procedures of a massive nature. Among radium-treated patients perhaps our urologic colleagues could be of more assistance to us in detecting impending leaks in the pelvic urinary system.

Severe sepsis and serious hemorrhage were factors in 40 per cent and 10 per cent, respectively, of our 2 series of patients. Both complications were twice as commonly encountered in patients of the old series as in patients of the new series. Contrastingly, thromboembolic phenomena, which occurred at an incidence of 20 per cent, are a much greater danger today than they were twenty years ago. Dicumarol and other anticoagulants might be a more satisfactory answer to this challenge, were it not for the even more formidable specter of hemorrhage.

Residual deposits of carcinoma were found in the uterus in 44 per cent and in the pelvis in 80 per cent of our patients, there being no difference in the number furnished by the two series studied. However, involvement of periaortic nodes (45 per cent) and of liver, lungs, bones, peritoneum and so forth, was twice as commonly noted among the patients more recently coming to necropsy than among earlier ones.

It becomes apparent, therefore, that we have succeeded in prolonging the lives of patients in whom the treatment of cervical cancer has not been followed by arrest of the malignant process. In doing so we have inadvertently succeeded in raising the incidence of vesicovaginal fistula, intestinal obstruction, abdominal carcinomatosis with its bothersome ascites, and other complications. Forty-five per cent of the individuals concerned who come to necropsy exhibit cancer extending beyond the confines of the pelvis, and transplanting of the ureters increases rather than decreases this incidence of distant spread.

Many will support wholeheartedly the proposal of the authors to divert the urinary stream during the course of extensive pelvic operations for carcinoma of the cervix. However, the idea of such diversionary strategy carried out on an elective basis may not carry the same appeal. Some, for instance, might favor a natural, painless drift into uremic coma over the deliberate choice of a brief respite inevitably followed by carcinomatosis and cachexia. The essayists appear to prefer this latter choice—which time may well prove to be correct.

"The abyss is worth the leap, however wide,
If life, sweet life, is on the other side."

In the situation under discussion, life on the other side is short at best and not so sweet. As a philosophic pathologist, I should be inclined to leave the issue of surgical intervention to those who stand vigil at the bedside.

DR. WARD (Closing).—Of course, it should be pointed out that the cases which we have cited surgically were the cases with a poor outcome. There have been many other surgical cases in which the outcome, so far, is better. I would like to mention further that at Charity Hospital, where this series was obtained, our services are somewhat divided in respect to treatment of carcinoma of the cervix. One of the services leaves the patients completely alone, surgically speaking. Another gynecological service is doing extensive surgery (Wertheim and even Brunschwig operations) in selected cases. A number of Brunschwig operations have been done, and I am happy to report only one death which occurred during the years of our survey.

I think in a few years a comparison of the methods of handling these cases on the different services of the same hospital will be of considerable interest.

INFANT MORTALITY IN A VOLUNTARY HOSPITAL*

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FETAL mortality stands before the obstetrician as one of his greatest challenges. Maternal mortality has, by concerted effort, better training, and the introduction of transfusions, chemotherapy, and antibiotics, been reduced in many institutions to an almost irreducible minimum. It is with the purpose of an inventory of our fetal mortality, and the hope of provoking improvements that this analysis is made.

A review was made of 22,158 deliveries during the ten-year period from Jan. 1, 1941, to Dec. 31, 1950. Neonatal deaths during this period numbered 339, while there were 334 stillbirths. This represented a neonatal death rate of 1.5 per cent and a stillbirth rate of 1.5 per cent. All infants of more than 20 weeks' gestation and weighing 500 grams or more were included. To systematize this involved study, the neonatal deaths will be discussed first.

Neonatal Deaths

It is evident from Table I, which shows a breakdown of the neonatal mortality rate by years, that there has not been any significant change during the period studied. This rate ranges from a high of 1.9 per cent in 1946 and 1947 to a low of 1.1 per cent in 1945.

Table I. Neonatal Mortality by Years

YEAR	NO. OF DEATHS	NO. DELIVERIES	PER CENT
1941	15	1179	1.3
1942	24	1666	1.4
1943	32	1800	1.8
1944	24	1870	1.3
1945	21	1876	1.1
1946	44	2271	1.9
1947	51	2737	1.9
1948	42	2772	1.5
1949	42	2954	1.4
1950	44	3033	1.5

Mortality Rate Subsequent to Various Types of Delivery

An analysis of Table II reveals several significant facts. During the period analyzed, 1,218 sections were performed; 523 of these were repeat sections.[1] There were no maternal deaths associated with sections, while the over-all maternal mortality for this period was .045 per cent.

Of the 37 neonatal deaths associated with sections, 9 were associated with repeat sections. Significant is the fact that only one of these nine infants lost with repeat sections might be interpreted as being a full-term infant. The

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infant was delivered by repeat section of a diabetic mother at 37 weeks' gestation. He was an edematous 7 pound, 12 ounce infant with evidence of lung congestion and poor respirations. Postmortem examination revealed pulmonary edema, pulmonary congestion, and pulmonary hyaline membrane. This latter finding might bear out prematurity in spite of weight since it is a finding usually associated with prematurity. The fact that, except for the above-described case, all other neonatal deaths associated with repeat sections were of premature infants is exceedingly important. All operators must be impressed with the necessity of improving their judgment in selecting the date for performing the section. This fact is further brought out by analyzing the 8 neonatal deaths that occurred in this group.

1. One repeat section resulted in a premature infant who died of atelectasis.

2. A premature infant who died due to a combination of prematurity and erythroblastosis was the result of a poorly timed section.

3. Pre-eclampsia led to an early section with death of the infant due to prematurity.

4. Cesarean sections performed for abruptio placentae with severe hemorrhage caused 2 fetal deaths, one from prematurity and one from erythroblastosis.

5. One patient with essential hypertension, toxemia, nephritis, and a previous bilateral sympathectomy was sectioned early and the infant died of hyaline membrane.

6. One patient with diabetes and pyelonephritis was sectioned early as a result of acute polyhydramnios and the infant died of emphysema, hydropericardium, and ascites.

7. One case of placenta previa with hemorrhage necessitated early section. The infant expired due to prematurity.

Only 1 and 2 were clearly cases of errors in judgment with resultant small infants who died during the neonatal period. Case 3 is questionable. It is the opinion of most well-trained obstetricians that the pre-eclamptic should be treated by both temporizing and supportive therapy, if possible, to prepare the mother better, as well as to permit the infant to become more mature. This infant might have been salvaged had this program been carried out.

The remaining 5 cases presented complications that necessitated prompt intervention in spite of the possible death of the fetus.

TABLE II. NEONATAL MORTALITY SUBSEQUENT TO VARIOUS TYPES OF DELIVERY

TYPES OF DELIVERY	NO. DELIVERIES	NO. DEATHS	PERCENTAGE	NO. DEATHS IN INFANTS OVER 2,500 GRAMS	PERCENTAGE
Cesarean section	1,218	37	3.0	7	0.57
Repeat cesarean section	523	9	1.7	1	0.19
High forceps	63	3	4.8	2	3.2
Version and extraction	79	12	15.2	3	3.8
Midforceps	565	6	1.1	6	1.1
Over-all series	22,158	339	1.5	80	0.36

Another significant fact revealed in Table II was the evidence that version and extraction carried a higher infant mortality rate, 15.2 per cent, than any other type of delivery. Second to version and extraction in causing neonatal death was the high forceps, 4.8 per cent. Of interest also is the fact that, for the mature infant, midforceps had a higher mortality rate than cesarean section, 1.1 per cent as compared to 0.57 per cent. The reverse appears to be true for the premature infant.

Causes of Death

Table III lists the causes of death. Many infants presented multiple causes of death, all of which were included. Thus the percentages as given in these tables add up to more than 100 per cent. Prematurity was listed in addition

to the other apparent causes of death, since it was usually impossible to rule it out as a contributing factor in the death of the infant.

Prematurity, present in 71 per cent of the cases, was by far the most common factor contributing to neonatal mortality. Pathology of the respiratory tract followed with an incidence of 23 per cent. This included bronchopneumonia, aspiration, atelectasis, hydrothorax, hemorrhagic congestion, and pulmonary hyaline membrane. Significant antepartum bleeding was present in 15 per cent of our series. This was diagnosed as abruptio placentae in 24 cases, placenta previa in 20, and undiagnosed in the remaining 6. There were 14 per cent congenital anomalies, contributing in varying degrees to the death of the infant. Twins were fourth, occurring in 14 per cent of the cases. This factor was evaluated more carefully, and the interesting conclusion was reached that the mortality rate for twins was 10.6 per cent, 46 of 433 twins, or 7 times the mortality rate for all infants. It was also of interest to note that prematurity was a factor in every one of the twins who was lost. Twenty of these twins were the first born and 26 the second born. This may indicate danger in version and extraction on second twins, since our study of this procedure showed 5 second twins lost subsequent to delivery by version and extraction. Twelve per cent of the babies showed asphyxia neonatorum.

TABLE III. CAUSES OF DEATH

CAUSE	NO. OF CASES	PER CENT
Prematurity	239	71
Pathological conditions of respiratory tract	78	23
Pulmonary hyaline membrane	13	4
Congenital anomaly	48	14
Anencephalic 2		
Hydrocephalic 4		
Twins	46	14
Bleeding, ante partum	50	15
Asphyxia	41	12
Toxemia of pregnancy	16	5
Difficult delivery	15	4
Erythroblastosis fetalis	17	5
Intracranial injury	12	4
Unexplained death of term infant	2	0.6
Prolapsed cord	4	1.2
Diabetes mellitus (maternal)	4	1.2
Rheumatic heart disease (maternal)	2	0.6
Erysipelas	1	0.3
Undiagnosed anemia (hemoglobin 26 per cent)	1	0.3
Abdominal pregnancy	1	0.3
Acute rheumatic fever (maternal)	1	0.3
Lobar pneumonia (maternal)	1	0.3
Hemorrhagic diathesis	1	0.3
Acute enteritis with peritonitis	1	0.3
Agranulocytosis with anuria (maternal)	1	0.3
Fatty metamorphosis of liver	1	0.3
Fatty metamorphosis of myocardium	1	0.3
Siamese twins	1	0.3
Bilateral adrenal hemorrhage	1	0.3

There then followed a group of factors intermediate in frequency composed of erythroblastosis fetalis, toxemia of pregnancy, difficult delivery, and intracranial injury. A final group of miscellaneous causes of death included such unusual conditions as abdominal pregnancy, a bizarre case of convulsions associated with agranulocytosis and anuria (in the mother), and Siamese twins.

Analysis of the causes of death in infants weighing more than 2,500 grams (Table IV) revealed that antepartum bleeding less commonly proved fatal to

the infant; difficult delivery and intracranial injury were almost exclusively limited to this group, and, as noted above, twins contributed to infant mortality only as they predisposed to premature labor.

Time of Death.—Our findings with regard to time of death of the infant confirm the findings of others that the longer the infant lives the better are his chances of ultimate survival. Sixty-one per cent of our series lived less than 24 hours, 85 per cent lived less than 2 days.

TABLE IV. CAUSES OF DEATH IN INFANTS OVER 2,500 GRAMS

CAUSE	NO. OF CASES	PER CENT
Pathological conditions of respiratory tract	34	42
Congenital anomalies	21	26
Asphyxia	22	27
Difficult delivery	15	19
Erythroblastosis fetalis	12	15
Intracranial injury	9	11
Bleeding (ante partum)	7	9
Abruptio placentae 5		
Placenta previa 2		
Toxemia of pregnancy	4	5
Rheumatic heart disease (maternal)	2	3
Unexplained	2	3
Prolapsed cord	1	1
Unexplained anemia (hemoglobin 26 per cent)	1	1
Hemorrhagic disease of newborn	1	1
Fatty metamorphosis of liver	1	1
Diabetes mellitus (maternal)	2	3
Bilateral adrenal hemorrhage	1	1

Autopsies were done on 33 per cent of the infants who died in the neonatal period. Our findings refute the frequently encountered impression that there is not much of value to be found in such examinations. On the contrary, records show that significant and instructive pathological conditions were found in 75 per cent of these infants, exclusive of prematurity and atelectasis.

Average Age and Parity of Mother.—The average age and parity of the mothers in this series were compared with the average age and parity of a representative group of patients admitted to our maternity service. The average age was found to be identical in the two groups, namely, 28 years. Primiparas were found to represent 49 per cent and multiparas 51 per cent of our admissions, whereas, in our present series, 42 per cent were primiparas and 58 per cent multiparas. This is not a large difference, but perhaps indicates some increase in fetal loss in the multipara.

Stillbirths

Table V shows the percentage of stillborn infants broken down into yearly segments. There is perhaps some evidence of a gradual decline in stillbirths

TABLE V. STILLBIRTH RATE BY YEARS

YEAR	NO. STILLBIRTHS	NO. DELIVERIES	PER CENT
1941	22	1,179	1.9
1942	31	1,666	1.9
1943	41	1,800	2.3
1944	34	1,870	1.8
1945	31	1,876	1.7
1946	32	2,271	1.4
1947	38	2,737	1.4
1948	35	2,772	1.3
1949	36	2,954	1.2
1950	33	3,033	1.1

during the years studied. This varied from a high of 2.3 per cent in 1943 to a low of 1.1 per cent in 1950.

Here again (Table VI) the safety of repeat cesarean section for the mature baby is apparent, there being only one stillbirth in 523 repeat cesarean sections. This was a case of abruptio placentae with the baby dead prior to surgery, which was done to save the mother. Version and extraction carried a high mortality, resulting in death for 6 mature infants alive at the beginning of the procedure, a 7.6 per cent mortality for the entire series. As with the neonatal deaths, the midforceps operation resulted in death only for mature infants.

TABLE VI. STILLBIRTH RATE IN VARIOUS TYPES OF DELIVERY

TYPE OF DELIVERY	NO. DELIVERIES	CONDITION OF BABY AT INCEPTION OF PROCEDURE	NO. STILLBIRTHS	%	NO. STILLBIRTHS IN INFANTS OVER 2,500 GRAMS	%
Cesarean section	1,218	alive	7	0.6	4	0.3
		dead	15	1.2	8	0.7
Repeat cesarean section	523	alive	0	0	0	0
		dead	1	0.2	1	0.3
High forceps	63		0	0	0	0
Version and extraction	79	alive	7	8.9	6	7.6
		dead	10	12.7	3	3.8
Midforceps	565	alive	9	1.6	9	1.6
		dead	6	1.1	5	0.9
Over-all series	22,158		334	1.5	137	0.6

Causes of stillbirths are found to be similar to the causes of neonatal death with the following major differences (Table VII): Prematurity plays a minor role. Most otherwise normal premature infants survive labor and delivery even though they may subsequently succumb. Respiratory pathology does not appear to enter into the problem. The major consideration is death of the infant prior to admission of the mother to the hospital for reasons which are not apparent.

TABLE VII. CAUSES OF STILLBIRTHS

CAUSE	NO. CASES	%
Unexplained death prior to admission	69	21
Congenital anomaly	56	17
Anencephalic 22		
Hydrocephalic 20		
Bleeding, ante partum	52	16
Toxemia of pregnancy	31	9
Intrauterine asphyxia	28	8
Difficult labor and/or delivery	22	7
Twins	19	6
Unexplained death after admission	20	6
Placental abnormalities	16	5
Prematurity (as definite factor in death, usually during labor or delivery)	12	4
Prolapsed cord	14	4
Erythroblastosis fetalis	13	4
Maternal infection	3	0.9
Intracranial hemorrhage	3	0.9
Trauma to mother	2	0.6
Diabetes mellitus (maternal)	2	0.6
Fractured skull	2	0.6
Maternal death with postpartum cesarean section	1	0.3

Congenital anomalies, bleeding, toxemia, asphyxia, twins, difficult labor, and/or delivery play equally important roles as major factors in the causation of both neonatal deaths and stillbirths. Placental abnormalities have seemed to explain more stillbirths than neonatal deaths. Fatal prolapse of the cord has

usually caused death before delivery can be accomplished. Erythroblastosis fetalis accounts for about as many stillbirths as neonatal deaths. Here, as in the other series, one notes the marked discrepancy between potential erythroblastosis and the number of fatal cases actually found. Thirteen per cent of marriages involve Rh-negative wives and Rh-positive husbands.[2] This would mean 2,881 such mothers in our series. There were 17 neonatal deaths and 13 stillbirths from erythroblastosis fetalis or one for every 96 Rh-negative mothers with Rh-positive husbands. Thus much hope can be held out to the average Rh-negative gravida.

Table VIII shows, as with neonatal deaths, that difficult labors and deliveries fatal to the infant are almost exclusively in this group. Unexplained death prior to admission, bleeding, congenital anomalies, asphyxia, and toxemia are about equally important as causes of stillbirth in mature as in premature infants. Twins showed an over-all stillbirth rate of 4.4 per cent (19 of 433 twins) with a rate of 1.6 per cent for mature twins. This is about 3 times the general stillbirth rate for these 2 groups. The 7 mature stillborn twins were the only mature twins lost out of a total of 433 twins and further support the contention that twins contribute to fetal wastage chiefly by virtue of predisposing to premature labor. Erythroblastosis fetalis caused no stillbirths among mature infants.

TABLE VIII. CAUSES OF STILLBIRTH IN INFANTS OVER 2,500 GRAMS

CAUSE	NO. OF CASES	PER CENT
Unexplained death prior to admission	29	21
Difficult labor and/or delivery	20	15
Asphyxia (mostly from cord compression)	23	17
Bleeding, ante partum	18	13
Abruptio placentae 16		
Placenta previa 2		
Congenital anomalies	18	13
Unexplained death after admission	11	8
Twins	7	5
Toxemia	6	4
Prolapsed cord	7	5
Placental disease	4	3
Diabetes mellitus (maternal)	2	1
Maternal death with postpartum cesarean section	1	0.7

Time of Death (Table IX).—More than half of our stillbirths involved death of the infant prior to the mother's admission to the hospital. In the next largest group, the infant died during delivery. Fifteen out of 35, or 43 per cent, of these deaths during delivery were associated with midforceps delivery or version and extraction.

TABLE IX TIME OF DEATH

TIME	PER CENT
Prior to admission	60
During delivery	13
Late in labor	7
During labor	6
Early in labor	5
Undetermined (e.g., twin)	5
Prior to labor	3
Prior to cesarean section	2

Autopsies were done on 24 per cent of our stillborn infants. Sixty-five per cent of these were productive of useful information other than obvious maceration and/or prematurity.

Average Age and Parity of Mother.—Mothers whose children were stillborn were found to average 29.5 years of age as compared with a hospital average of 28 years. Primiparas and multiparas occurred in a ratio of 49:51, which corresponds exactly with the hospital average.

Maturity.—In contrast to neonatal death, where the ratio of premature to mature infants is 76:24, stillbirths were found to include 41 mature infants. Thus nearly twice as many mature infants died prior to delivery as did so in the neonatal period. We previously pointed out that neonatal death occurred in decreasing degree as time passed subsequent to delivery. Here it becomes apparent that the increased danger of death as one travels back toward birth extends right on through the time of birth, so that, for the term infant, the period of labor and delivery, and the time immediately preceding it are even more dangerous than the most dangerous first day of life.

Summary and Conclusions

1. The neonatal mortality and stillbirth rates for the years 1941 through 1950 at Milwaukee Hospital have been 1.5 per cent in both instances.

2. Graphic comparison of neonatal mortality and stillbirth rates at Milwaukee Hospital with those in the city of Milwaukee and the state of Wisconsin is shown in Figs. 1 and 2.

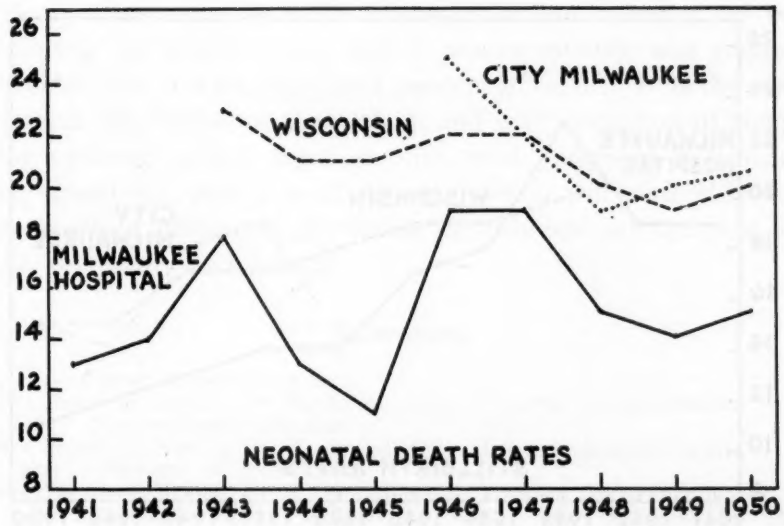

Fig. 1.

It is apparent that the rates at Milwaukee Hospital have been consistently superior to those in the city of Milwaukee and the state of Wisconsin.[3]

Comparison with figures from Chicago Lying-in Hospital for the period July 1, 1941, to July 1, 1946, with correction made to include only infants over 1,000 grams as in the Chicago report follows: neonatal mortality at Milwaukee Hospital (1941 to 1950) was 1.19 per cent and at Chicago 1.24 per cent. Corresponding stillbirth rates were 1.27 per cent and 1.25 per cent. Comparisons may be seen to be quite favorable.[4]

3. The most common causes of neonatal death were prematurity, respiratory pathology, antepartum bleeding, congenital anomaly, twins, and asphyxia neonatorum. In the mature infant, difficult delivery and intracranial injury became more important and antepartum hemorrhage less so.

4. Elective cesarean section as represented by our repeat cesarean sections has no demonstrable infant mortality *provided* that prematurity of the infant be avoided by good judgment. Only one questionably mature infant of a diabetic mother was lost in this series.

The properly timed, well-executed primary cesarean section may often materially reduce infant mortality without maternal hazard as evidenced in this series. This, however, may have to be done at the expense of an increased cesarean section incidence at times.

5. Version and extraction have the highest infant mortality rate, followed by high and midforceps. For the mature infant, midforceps has a higher mortality rate than cesarean section, but the reverse appears to be true for the premature infant.

An operative delivery must be viewed with proper respect, since the neonatal death rate is directly dependent upon the care and judgment exercised in employing the choice of maneuver and the management of forceps.

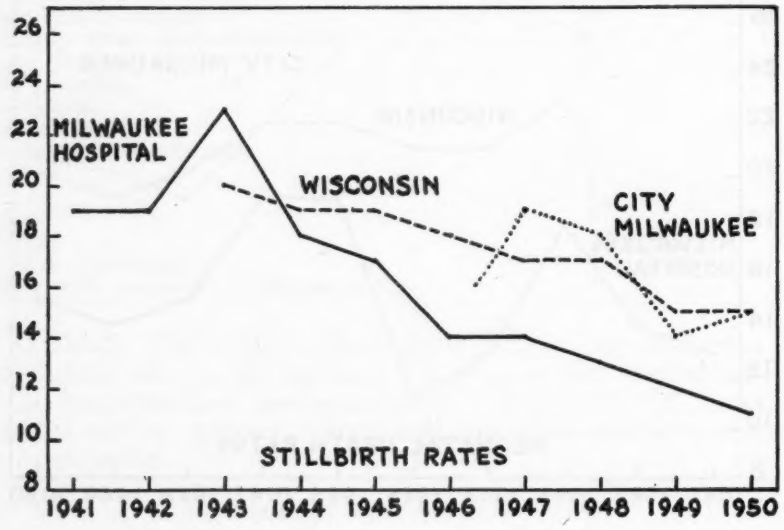

Fig. 2.

6. The neonatal mortality rate in twins was 7 times as great as the over-all neonatal mortality rate and seemed to be entirely accounted for by the tendency to premature labor in twin pregnancy.

7. The most common causes of stillbirth were unexplained fetal death prior to the mother's admission to the hospital, congenital anomalies, antepartum bleeding, toxemia of pregnancy, intrauterine asphyxia, difficult labor and/or delivery, twins, and placental abnormalities.

The over-all causes of infant loss were obtained by combining neonatal deaths and stillbirths. Prematurity was a contributing factor in 25 per cent

of the cases. This, plus congenital anomaly and antepartum bleeding, accounted for essentially one-half of the deaths. Asphyxia, respiratory pathology, unexplained death prior to admission and twins make up the third 25 per cent. The final 25 per cent is found to include toxemia, difficult labor and/or delivery, erythroblastosis, and a group of miscellaneous infrequent conditions. Prematurity remains one of the greatest hurdles to all infants and to the efforts of all obstetricians.

9. Fatal erythroblastosis fetalis occurred in only 1 per cent of infants with Rh-negative mothers and Rh-positive fathers. For Rh-negative mothers, this should be very encouraging. The physician, however, should not discount the importance of the problem since erythroblastosis fetalis is high on the list of treatable diseases causing fetal mortality. Many of the more common conditions are little altered by treatment.

10. Almost twice as many mature infants were stillborn as succumbed in the neonatal period. A term infant born alive had already cleared the highest hurdle.

11. Close cooperation must exist between the pediatrician and the obstetrician, with the obstetrician aware and informed of the problems existing in the nursery during the neonatal period, if the infant death rate is to be reduced.

12. Every effort must be made to emphasize the necessity for impressing students during the clinical years with a proper attitude and respect for accurate prenatal care and an intelligent conduct of labor. It is the combination of diet, careful observation of the patient, and early detection of complications during the prenatal period, together with good judgment in premedication, anesthesia, episiotomy, and type of delivery, which will materially reduce the premature onset of labor and determine the ultimate salvage rate of mother and infant, premature and mature.

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Discussion

DR. ROBERT L. NEWMAN, Kansas City, Kan.—We are indebted to Dr. Hofmeister for presenting a subject which cannot be discussed too frequently. The importance of fetal mortality cannot be overstressed, particularly when we realize, as pointed out in the presentation, that fetal mortality figures have not kept pace with the decline in maternal mortality during the past decade. There may well be an irreducible minimum of fetal deaths represented, perhaps, by such causes as gross congenital abnormalities, but no one has, as yet, approached that irreducible minimum.

Our own figures, from the Medical Center of the University of Kansas, show 154 fetal deaths in 5,604 consecutive deliveries with a fetal mortality rate of 2.7 per cent. One-half of these deaths occurred prior to delivery and one-half were neonatal deaths. These figures are offered for comparison with those of Dr. Hofmeister. We believe that these percentages

are still too high and offer as a partial alibi the fact that many of our own cases are referred to the hospital only after the pathology is well developed, or the baby already dead.

The problem of fetal mortality is made complex by the multiplicity of factors involved. For example, most are agreed that obstetrical anesthesia and analgesia have a definite effect on fetal mortality. Masters and Ross would seem to have demonstrated marked reduction in fetal deaths with use of conduction anesthesia. I am wondering what anesthesia and analgesia were used for the delivery of the patients in the series presented to us and if some of the deaths included in the prematurity, asphyxia, and respiratory pathology groups could be attributed to this cause.

The high incidence of fetal mortality associated with midforceps and version operations is striking, particularly when compared to the fetal mortality in cesarean section. Almost all fetal deaths in the latter situation are due to associated pathology requiring the surgery. Does this mean that the midforceps operation is an outmoded procedure, and, when its use is required, indicates an error in obstetrical judgment? Perhaps it should be largely discarded as the high forceps operation has been.

One of the most obvious features of any study of fetal mortality is the greatly increased death rate in the premature or immature infant, underlining the fact that our efforts should always be directed toward carrying the pregnancy to at least the thirty-second week, if possible, without too great danger to the mother, in any patient with toxemia, antepartum bleeding, and the like.

Obviously then, the important factors in fetal death contain a man-made element of which we must always be conscious.

The problem will be improved with careful pathological studies of all, not part, of the fetal deaths and thorough discussion of each death at the local level.

DR. HOFMEISTER (Closing).—I wholeheartedly feel that there is much to be desired in an attempt to reach the irreducible minimum in fetal deaths. There is very little difference in our stillbirth and neonatal death rates as evidenced by the figures quoted by Dr. Newman.

In the last two years we at Milwaukee Hospital have attempted by hard and fast rule to deliver all premature infants by conduction anesthesia. The usual form of anesthesia in all cases varies between gas-ether in the greater percentage and saddle block in the lesser group.

Analgesia employed in our hospital varies with the individual doctor assuming the responsibility of the case. Since this is a private institution the attending doctor has his choice of the conduct of labor.

There is no question in our minds that some of the deaths included in the prematurity, asphyxia, and respiratory pathology groups could be attributed to the anesthesia and analgesia used, especially in those cases included in the early years of this series.

I do not believe that we can go so far as to say that the midforceps operation is an outmoded procedure, or that it should be discarded. It is my feeling that serious consideration of cesarean section should be given when a complicated midforceps delivery is anticipated. One wonders at times whether we are not too prone to direct our activities in the light of possible resultant statistics.

We are in complete accord that good judgment is the very essence of good obstetrics and this can only be good if a low maternal and fetal mortality results.

All infants must be carefully judged as to size and maturity before an operative delivery is performed. Whenever possible, procedures should be put off so that time required for maturity and size can be gained to insure safety to the infant.

As was evidenced in our paper, the pathological studies on a large number of infants who were stillborn or who died in the neonatal period show a high incidence of contributory conditions which could not have been recognized without these studies.

A CORRELATION OF THE CYTOLOGY OF THE URINARY SEDIMENT WITH ENDOMETRIAL HISTOLOGY*

E. STEWART TAYLOR, M.D., AND PAUL F. MCCALLIN, M.D., DENVER, COLO.

(From the Department of Obstetrics and Gynecology, University of Colorado School of Medicine)

IN A previous paper we[1] have reported changes in the cytology of the urinary sediment that correspond to various levels of estrogen and progesterone during the female reproductive cycle. Others[2, 3] have also studied the morphology of the desquamated cells of the urinary tract in relation to hormonal variations. Papanicolaou[2] was the first to recognize the influence of estrogen upon such cells. South American workers[3] have placed the emphasis upon changes in cells from the anterior urethra, while we have studied cells from the bladder and upper urinary tract.

The present study is concerned with a correlation of the cytology of the urinary sediment with the morphology of the endometrium in various normal and pathological states. It is our purpose to demonstrate the response of the urinary smears to the cyclical variations of the female reproductive life by comparison with tissue sections of endometrium obtained at the same time. This study also gives some insight into the hormonal variations in certain pathological states.

Methods

A total of 53 patients were studied, including 27 women with normal menstrual cycles and 8 postmenopausal women. Pathologic states included 7 patients with anovulatory bleeding, 4 with endometrial hyperplasia, 5 with adenocarcinoma of the uterine fundus, one with ectopic pregnancy, and one with a masculinizing tumor of the adrenal.

Specimens of endometrium were obtained by dilatation and curettage of the uterus except in two instances where endometrial biopsies were obtained by means of a Novak curette. At the time of the curettage a catheterized urine specimen was obtained. The urine (60 c.c.) was centrifuged, and the sediment was smeared and stained by a modification of Papanicolaou's method.[4]

Results

1. Normal Menstrual Cycle.—

Of the 27 endometrial specimens from women with normal menstrual cycles, 8 were classified as proliferative, 3 as midinterval, and 16 as secretory. By following the criteria reported in our previous paper the urinary smears correlated with the endometrial histology in all cases. The proliferative smear generally showed scattered and small clusters of superficial epithelial cells with pyknotic nuclei and cytoplasmic granules and vacuoles (Fig. 1). The midinterval smear showed more prominent clustering of cells with even more noticeable nuclear pyknosis and cytoplasmic granules (Fig. 2). Intermediate epithelial cells with vesicular nuclei and moderately homogeneous cytoplasm were

*Presented at the Nineteenth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Detroit, Mich., Sept. 20, 21, and 22, 1951.

more numerous. In those urinary smears taken from women during the secretory phase of the menstrual cycle, large numbers of cell clusters with marked cellularity were seen. In these women the endometrium showed normal premenstrual changes. Superficial urinary tract cells had pyknotic nuclei and cytoplasmic granules. The intermediate cells were more numerous and demonstrated clustering and wrinkling with mixed vesicular and pyknotic nuclei (Fig. 3). It was not possible to correlate changes in the urinary smear to the actual day of the cycle, but all smears did fall into one of the above categories as determined by study of the endometrium. No disagreement between endometrial sections and urinary sediment smears was observed.

2. Anovulatory Bleeding.—

Specimens were obtained for study from seven women who were bleeding from a proliferative endometrium. The urinary smears resembled smears taken at about the mid-portion of the normal proliferative phase (Fig. 4). An average smear consisted of scattered superficial cells with some cytoplasmic granulation and nuclear pyknosis with no changes associated with the presence of progesterone.

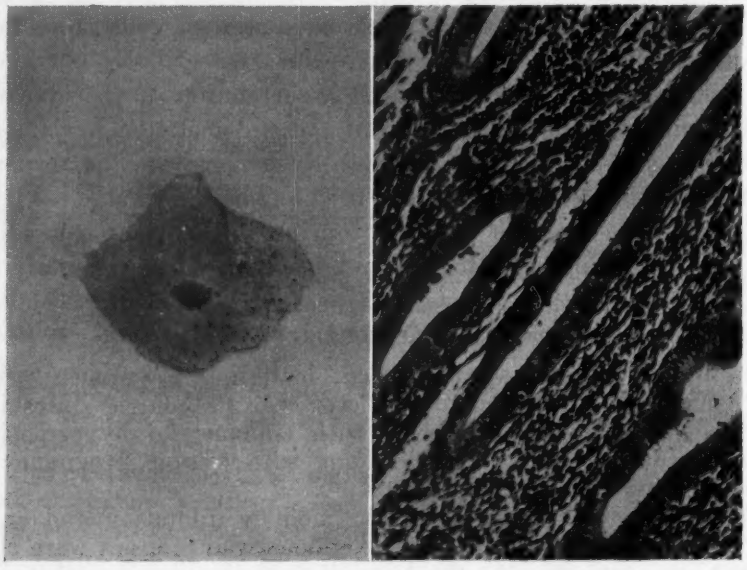

Fig. 1.—Proliferative endometrium and urinary smear showing a single superficial cell with cytoplasmic granules and moderate nuclear pyknosis.

3. Endometrial Hyperplasia.—

Smears were obtained from four women whose endometrium showed the typical changes described as hyperplasia. These smears resembled those from the women with anovulatory bleeding, although the changes ascribed to presence of estrogen were more prominent. The cells of the urinary tract were more acidophilic with numerous cytoplasmic granules and pyknotic nuclei. There was a predominance of superficial cells and a paucity of the intermediate forms (Fig. 5) which are typically found in smears from women who show considerable estrogen and minimal progesterone effect in the endometrium.

4. Adenocarcinoma of the Uterus.—

Urinary smears were obtained from five women whose curettings revealed adenocarcinoma of the endometrium. Four of these patients were two or more years beyond the menopause at the time the diagnosis was made. The urinary sediment smears from the four postmenopausal women revealed no estrogen

effect, suggesting that prolonged estrogen stimulation did not accompany adenocarcinoma of the endometrium in these patients (Fig. 6). Smears from one patient revealed mild estrogen effect as evidenced by scattered superficial cells showing cytoplasmic granules and nuclear pyknosis. This patient had her last normal menstrual period one year previously and had been bleeding irregularly since that time.

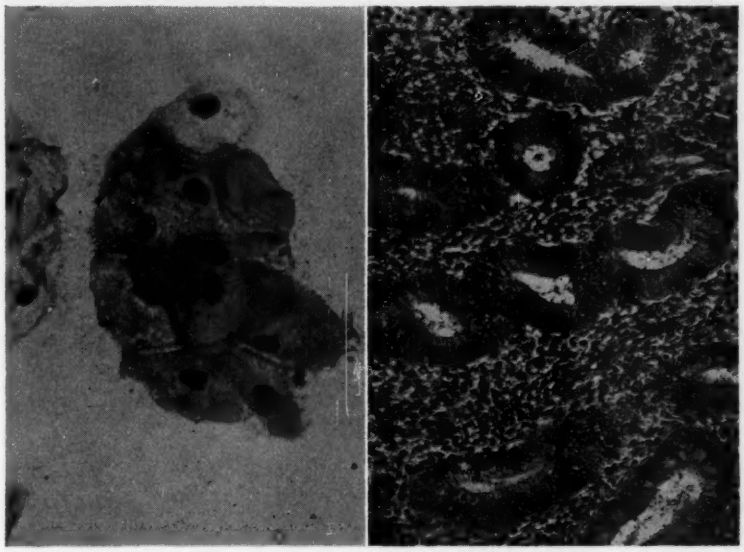

Fig. 2.—Midinterval endometrium and urinary smear showing clustering of superficial cells with considerable nuclear pyknosis.

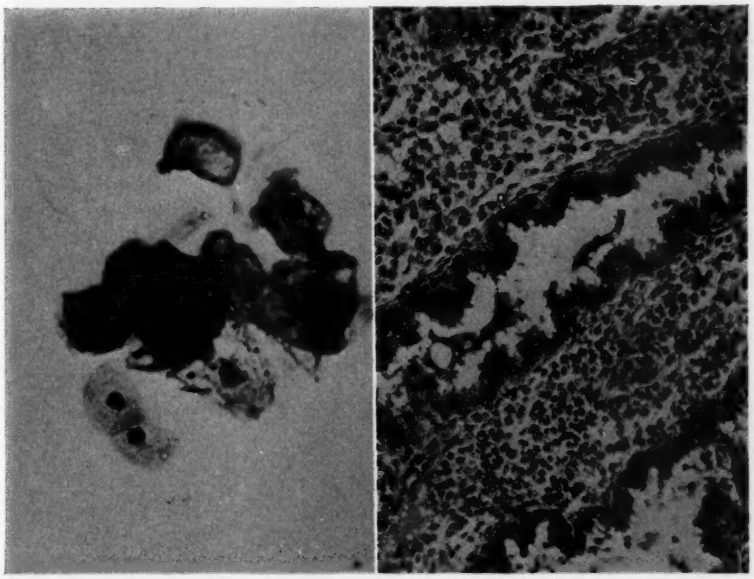

Fig. 3.—Secretory endometrium and urinary smear showing a cluster of superficial cells with cytoplasmic granules and nuclear pyknosis. Intermediate cells are seen above and below the cluster.

5. Atrophic Endometrium.—

Eight postmenopausal women were curetted and urinary smears were obtained at the time of operation. Histologic sections showed atrophic endo-

metrium and all smears showed findings consistent with a lack of hormonal stimulation. Only a few cells were seen in the specimens. These were variable in size but had large nuclei in relation to the amount of cytoplasm, the reverse of that seen in younger patients. Nuclei were a mixture of vesicular and granular types and the cytoplasm was homogeneous (Fig. 7). No large squamous-like cells characteristic of estrogen stimulation were observed.

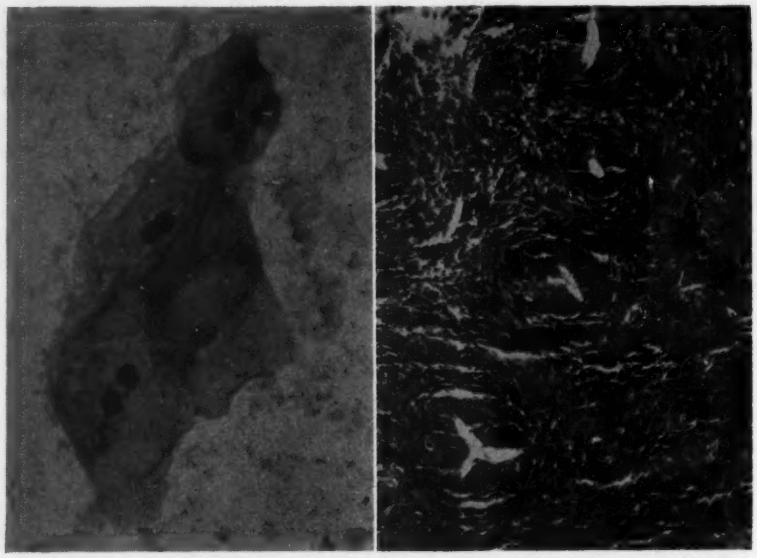

Fig. 4.—Nonsecretory endometrium and urinary smear showing a cluster of superficial cells with a moderate estrogen effect from a case of anovulatory bleeding.

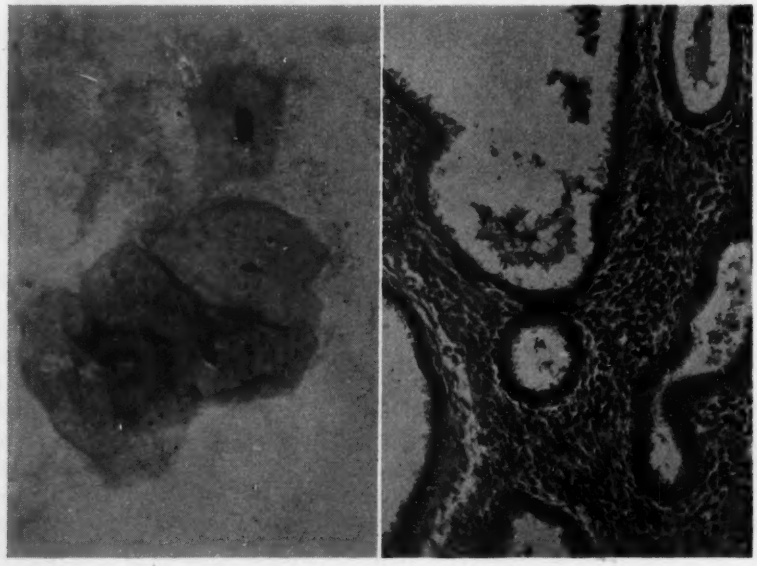

Fig. 5.—Hyperplastic endometrium and urinary smear showing superficial cells with more nuclear pyknosis and cytoplasmic granules than shown in Fig. 4.

6. Ectopic Pregnancy.—

It was possible to obtain endometrial tissue and urinary smears from only one patient with ectopic pregnancy. Laparotomy on the day of the curettement

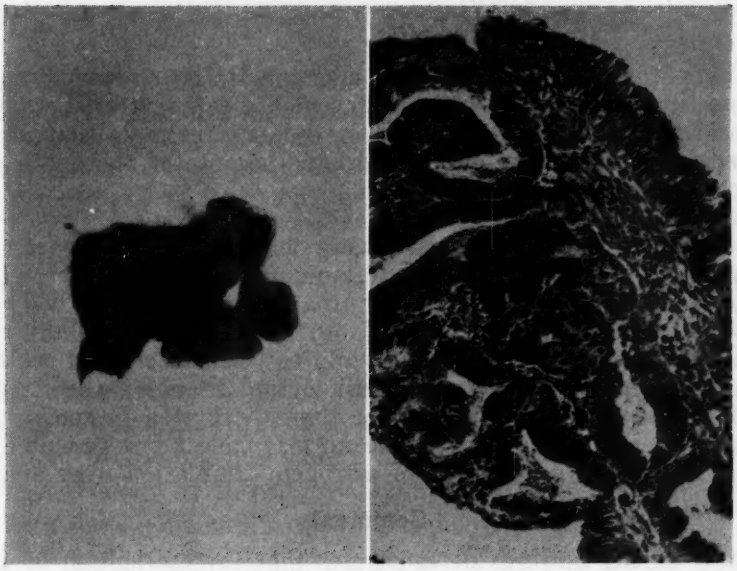

Fig. 6.—Endometrial carcinoma and urinary smear showing minimal hormonal stimulus from a postmenopausal woman.

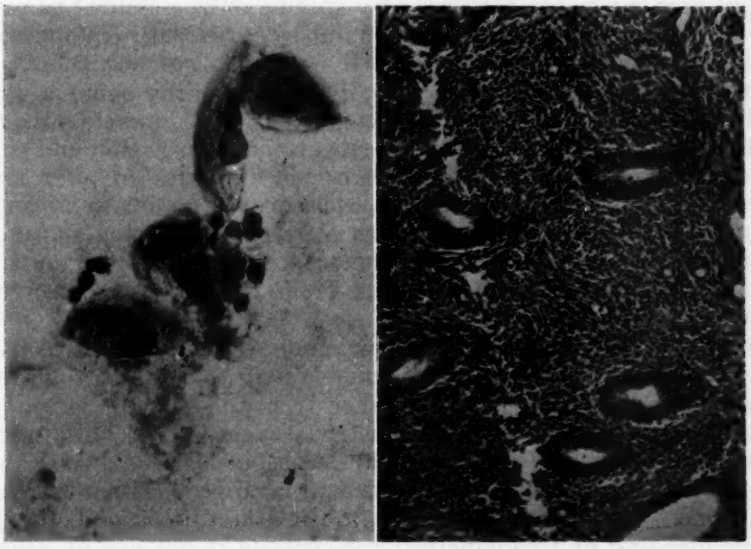

Fig. 7.—Atrophic endometrium and urinary smear showing minimal hormonal stimulus from a postmenopausal woman. Note the large nuclei in comparison to the total cell size. This is also seen in Fig. 6.

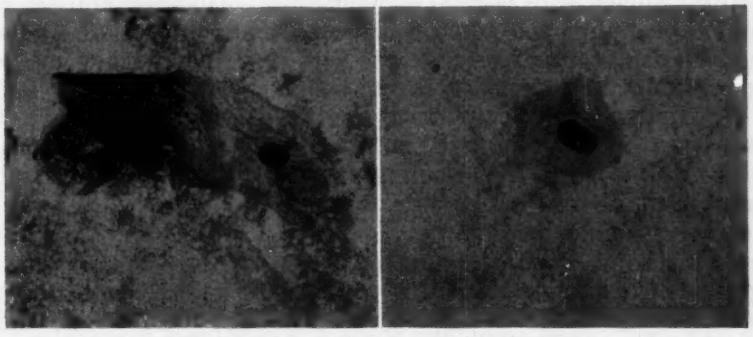

Fig. 8.—Superficial cell on the right is from a patient having a masculinizing tumor of the adrenal. On the left is a cluster of similar cells from the adult male urine.

revealed the pathology to be a tubal abortion. The endometrium showed a decidual reaction. The urinary smear revealed a few scattered superficial cells showing mild estrogen effect. The smear did not resemble that of pregnancy as described in our previous paper,[1] perhaps because of the death of the conceptus associated with the tubal abortion.

7. Masculinizing Tumor of the Adrenal.—

Urinary smears and endometrium were obtained from a 37-year-old woman who had a tumor of the right adrenal gland, 10 cm. in diameter. Her history revealed amenorrhea for five years with progressive increase of body hair, deepening of voice, atrophy of breasts, and other signs of a masculinizing tumor. The endometrium was quite atrophic while the smears showed scattered squamous-like cells with homogeneous basophilic cytoplasm and rather large granular nuclei. The cells were somewhat larger than those seen in smears from postmenopausal women, although cells from normal male urine resemble the above-described cells (Fig. 8). No signs of estrogen stimulation were evident.

Comment

A review of our findings demonstrates that the epithelium of the urinary tract responds to hormonal stimulation in a pattern that parallels endometrial activity. The urinary smear is not sufficiently specific to determine day-to-day changes, but any one smear is sufficiently specific to be classified as proliferative, midinterval, or secretory, and will be found to agree with endometrial sections obtained coincidentally.

The urinary smears obtained from women bleeding from a proliferative endometrium corresponded to the accepted view[5] that in such cases there is an absence of ovulation with a failure of corpus luteum formation and consequently no estrogen effect. Study of the urinary smear seems to offer an alternate method for determining the presence or absence of ovulation at any one particular monthly cycle. If ovulation has occurred a urinary smear made just before menstruation will reveal the characteristic mixture of superficial and intermediate epithelial cells that results from progesterone effect on urinary epithelium (Fig. 3).

In endometrial hyperplasia, the urinary smears showed rather marked estrogen effect, although no specific diagnostic feature could be found that would differentiate these smears in every instance from those in the latter part of the normal proliferative phase of the menstrual cycle. These findings, however, substantiate the view[6] that endometrial hyperplasia is associated with long-continued stimulation of the endometrium by estrogens without the interaction of progesterone. The smears also indicate that the difference between so-called anovulatory bleeding and endometrial hyperplasia is but one of degree.

The urinary smears in the postmenopausal woman with adenocarcinoma of the endometrium revealed no remarkable findings. They resembled smears from postmenopausal women with normal endometrium. Hodgson and her co-workers[7] in 62 cases of granulosa-cell tumors reported an incidence of 21 per cent co-existing endometrial carcinoma. It was felt that the urinary cytology might reveal hyperestrinism in women with endometrial carcinoma but such was not the case. Our finding would support the interpretation of Woll, Hertig, Smith, and Johnson[8] that signs of activity in the ovaries of women with endometrial carcinoma are due to stimulation of the anterior pituitary by tissue breakdown products rather than to a primary disorder of the ovary with resulting malignant changes in the endometrium.

The case of the masculinizing tumor of the adrenal is of interest merely because it gives further confirmation of the sensitivity of the epithelium of the urinary tract to the sex hormones. In this patient with a high androgen secretion, the smears resembled closely the urinary cytology of normal males.

The epithelium of the urinary tract and the oral epithelium are responsive to the sex hormones, illustrating that castration produces organic effects beyond those changes normally expected in the vagina, uterus, and breasts. It would seem, therefore, that conservation of normal ovarian tissue is desirable at least until complete atrophy of function.

Summary and Conclusions

Simultaneous catheterized urine specimens and endometrial biopsies were obtained from 53 women: 27 had normal menstrual cycles and 8 women had normal postmenopausal endometrium; the other specimens were from women with pathological conditions. Seven were classified as having had anovulatory bleeding, 4 had endometrial hyperplasia, 5 adenocarcinoma of the endometrium; one women had an ectopic pregnancy and one a masculinizing tumor of the adrenal. The cytology of the stained urinary sediment was then studied and correlated with the microscopic sections of endometrium.

In the 27 women with normal menstrual cycles and normal endometrium, the urinary smears could be classified as proliferative, midinterval, and secretory, and agreed in all cases with a similar classification of the endometrium.

Urinary smears from the postmenopausal women with atrophic endometrium showed lack of hormonal activity. The urinary cells in the postmenopausal women with endometrial carcinoma did not show any particular difference from smears of normal postmenopausal women.

Urinary smears from the women with anovulatory bleeding and endometrial hyperplasia showed the characteristics of estrogen stimulation. The difference between smears from the two groups was only one of degree.

The masculinizing tumor of the adrenal further substantiated the sensitivity of the urinary tract epithelium to sex hormones. Smears showed a resemblance to the normal male cytology rather than to any phase of the female reproductive cycle.

Cyclical changes in the cytology of the urinary sediment can be correlated with similar changes in the endometrium during the menstrual cycle. In pathological states of the endometrium, the urinary smears demonstrate no diagnostic features, although they do reflect hormonal alterations.

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Discussion

DR. PAUL F. FLETCHER, St. Louis, Mo.—A simple epithelium is one in which cells lie on the basement membrane in a single continuous layer. They may be squamous,

cuboidal, or columnar in type. Simple squamous epithelium is seldom found in the genital tract, but simple cuboidal and columnar epithelia may be found in the Fallopian tubes and endometrium. The endocervix is lined with a simple type of tall columnar epithelium.

When the number of cells forming an epithelium is increased to the point where it is no longer possible for each cell to rest on the basement membrane, the epithelium becomes stratified and for practical purposes forms three distinct layers:

A. The deep, or basal, layer is situated next to the underlying connecting tissue to which it is attached. It is composed of so-called inner and outer basal cells. These are the young forms.

B. Next is the transitional, or intermediate, layer composed of cells that are a little older and therefore somewhat larger and better developed.

C. The outer, or superficial, layer forms the surface epithelium. When cells from this layer die they are sloughed off, or desquamated, and become the so-called exfoliated epithelial cells. They are replaced by cells from the underlying intermediate layer, which in turn assume the characteristics of superficial cells. Cytologically speaking, there are two types of superficial epithelial cells: cornified and noncornified. True cornification is indicative of the amount of cytoplasmic glycogen present within the cell. The number and quality of cornified cells in a smear, when compared quantitatively with the noncornified cells present, are a fairly reliable criterion for evaluating follicular hormone activity associated with certain physiological and pathological phenomena.

Stratified squamous epithelium lines the vulva, vagina, and vaginal portion of the cervix.

Transitional epithelium is present in the urinary bladder, ureters, urethra, and kidney pelvis. In the female genital tract it is also found in the ducts of Bartholin's glands. It, too, is stratified and has three cell layers comparable to those seen in squamous epithelium; consequently, the epithelium of the urinary tract and female genital tract have much in common, cytologically. In view of these histologic facts, the assumption of a comparable response of urinary epithelial cells to the same influences which bring about cyclic changes in the vagina and endometrium is logical and sound.

Cytologic correlation of vaginal epithelium with cyclic changes in the endometrium was accomplished many years ago by Papanicolaou, Rubinstein, and others, but so far as I know this is the first time a relationship between the cytology of urinary sediment and endometrial histology has been demonstrated. The authors are to be commended very highly for the originality of their approach to this interesting problem, and for the meticulous care used in the conduct of their investigation. The objective evidence they have submitted to support their observations and conclusions is accurate and reliable and should be accepted as a genuine contribution to the relatively new and challenging science of exfoliative cytology.

DR. EDUARD EICHNER, Cleveland, Ohio.—Approximately two years ago we started a clinical experiment in pseudopregnancy on a group of normally menstruating women, with the purpose of producing ureteral dilatation by the use of hormones. This was done in one patient in the series.

During the follow-up of this group we did endometrial biopsies, vaginal and cervical spreads, urinary sediment studies, and work in other phases. I have one chart (Table I) showing, in a group of six patients, the comparison on the cornification counts of the cervix, vaginal pool, and urine sediment with the endometrial findings at that time.

This takes place over a period of six or seven months. This first column is our basic work done before the experiment started.

Here is a patient (No. 34780) with postovulatory, early secretory endometrium, and the urine sediment is almost identical with that in the vaginal pool.

Here is a premenstrual endometrium (No. 36467) with a marked progesterone effect, in which the urine sediment cornification count drops.

TABLE I. CORNIFICATION COUNTS

	DECEMBER, 1949	JANUARY, 1950	MAY, 1950
No. 34780			
Cornification:			
Cervix	14%	21%	20%
Vaginal Pool	23%	21%	17%
Urine	22%	3%	10%
Endometrium	Postovulatory, early secretory	Involuting decidua	Reparative and proliferative
No. 34687			
Cornification:			
Cervix	35%	34%	74%
Vaginal Pool	38%	30%	47%
Urine	18%	8%	22%
Endometrium	Glandular atrophy	Early decidua	Reparative and proliferative
No. 34376			
Cornification:			
Cervix	63%	68%	63%
Vaginal Pool	91%	54%	60%
Urine	40%	20%	5%
Endometrium	Postovulatory, early secretory	Decidua	Proliferative
No. 36467			
Cornification:			
Cervix	53%	71%	41%
Vaginal Pool	59%	52%	31%
Urine	9%	10%	12%
Endometrium	Late secretory, premenstrual	Decidua	Reparative and proliferative
No. 32617			
Cornification:			
Cervix	79%	23%	68%
Vaginal Pool	72%	15%	69%
Urine	12%	0	5%
Endometrium	Proliferative, glandular polyp	Decidua	Proliferative
No. 36469			
Cornification:			
Cervix	20%	12%	14%
Vaginal Pool	24%	7%	11%
Urine	5%	10%	10%
Endometrium	Late proliferative	Decidua	Reparative and proliferative

All endometria of May, 1950, showed varying degrees of "swiss cheese" glands.

Here is a proliferative one (No. 32617) in which the vaginal pool and the cervix are very high and the urine sediment does not agree.

Here is another late proliferative (No. 36469) in which the cervix and vaginal pool are a little high, but the urine count is remarkably depressed.

The next column is approximately one month later. At that time these patients were getting approximately 2,000 units of chorionic gonadotropin daily, 75 mg. of progesterone, and had already received approximately 100 mg. of estradiol by pellet implant.

The endometrium in all cases showed decidua of various types. The bottom four showed typical decidua. The pathologist who first saw these slides wanted to know where I had that many cases of ectopic pregnancy for endometrial biopsy on the same day. He was not in on the secret at the time. The others showed various degrees of decidua formation. The only thing noticeable is that the urinary sediment count in general dropped quite a bit, in one case down to zero.

The last column on the chart shows the sediment studies and the biopsies done ten days after the conclusion of the basic portion of the experiment. At that time none of the subjects was getting the complete series of drugs. All of them had already had 275 mg. of estradiol by implant. Some of these were receiving as high as 200 mg. of progesterone daily; some of them were receiving only chorionic gonadotropin. All the endometria were in the proliferative state, and a good many of them showed the typical "swiss cheese" of hyperestrinism.

The urinary sediments, as far as cornification is concerned at this stage, did not show as good a picture as the vaginal pool. I might say in passing that it is now over 18 months since the estrogen was implanted, and these patients still show "swiss cheese" endometrium. None of them was a castrate. They were all normally menstruating women at the start.

DR. TAYLOR (Closing).—Workers in South America noticed the hormone influence on urinary tract epithelium several years ago and published in the *American Journal of Endocrinology* a study of somewhat similar nature, done in a different manner.

The only advantage of a urinary sediment study of this type is that infection and blood are not present as they are in the vaginal smears that are used for studying various types of hormone responses and absences. This method may be proposed as an additional method for determining the presence or absence of ovulation, if the specimen is obtained just prior to the onset of menstruation.

THE RECOGNITION AND TREATMENT OF SOMATIC ABDOMINOPELVIC PAIN*

WILLIAM C. ELLER, M.D., F.A.C.S., WATERLOO, IOWA

A LARGE percentage of women complaining of abdominopelvic pain do not have any gynecologic disease. Yet, in a seeming zeal to "find a lesion to explain a symptom," any palpable deviation from normal on pelvic examination, however minor, has frequently been seized upon as the cause of the trouble, without any effort to look elsewhere for an explanation. And so the error is perpetuated, and the patient takes her pain elsewhere, sometimes without having had unnecessary pelvic surgery.

On the other hand, it is hardly sufficient in the eyes of the patient to make the purely academic observation that her "female organs" are normal, and let it go at that. Some relief of her complaint must be offered, whether it be correct treatment or the intelligent referral of her case into the proper hands. And so an understanding of the extragenital causes of pelvic pain becomes mandatory for the gynecologist, as well as the general practitioner.

The orthopedic, urologic, intestinal, and psychosomatic causes of pelvic pain have been emphasized elsewhere.[1] The purpose of this presentation is to direct attention to another cause of abdominopelvic pain, which has received little attention in gynecologic literature: pain which is somatic—not visceral—in origin. Various terms have been applied to this symptom complex: abdominal wall neuralgia, segmental neuralgia,[2] neurogenic pain.[3] All have reference to the syndrome of pain and tenderness which originate, not within the abdominal viscera, but in some irritative lesion of the spinal nerves which supply the abdominal wall. For example, the patient may complain of pain in the right lower quadrant, but adequate examination will reveal a very characteristic type of tenderness over that part of the abdominal wall supplied by the twelfth dorsal and first lumbar nerves. Fig. 1 illustrates the distribution of a typical spinal nerve with special reference to the posterior, lateral, and anterior cutaneous branches. The skin sensory segments—or dermatomes—of the spinal nerves supplying the lower abdominal wall are diagrammatically represented in Fig. 2.

This combination of somatic pain and tenderness is due to irritation of the nerve roots, ganglia, or nerve trunks, either primary or as a result of disease of the soft structures near the vertebral column. There are many underlying causes for this nerve-trunk irritation: infectious, postural, traumatic, arthritic. At any rate, the causative lesion is nowhere near the area of pain described by the patient, nor in any underlying organ; but rather in or near

*Presented at the Nineteenth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Detroit, Mich., Sept. 20, 21, and 22, 1951.

the vertebral column. Frequently the specific origin cannot be demonstrated. Yet symptomatically most of these patients can be given lasting relief of their pain, so that, from the standpoint of treatment, somatic pain or segmental neuralgia may be considered a clinical entity.

Certain fundamental points are of interest in the understanding of this syndrome: (1) There is no subjective difference at all in the quality or localization between somatic and visceral pain.[5] (2) Injecting the site of pain with procaine does not relieve the pain of segmental neuralgia—nor, obviously, does the removal of any underlying organ, normal or otherwise. (3) Conversely, procaine injection of nerve trunks supplying the right lower quadrant does not relieve the pain and tenderness of visceral disease, such as appendicitis or salpingitis. (4) Improvement or cure of somatic tenderness and pain does follow treatment directed at the spine, by postural correction, diathermy, or, more specifically, paravertebral procaine block of the corresponding nerve trunks.

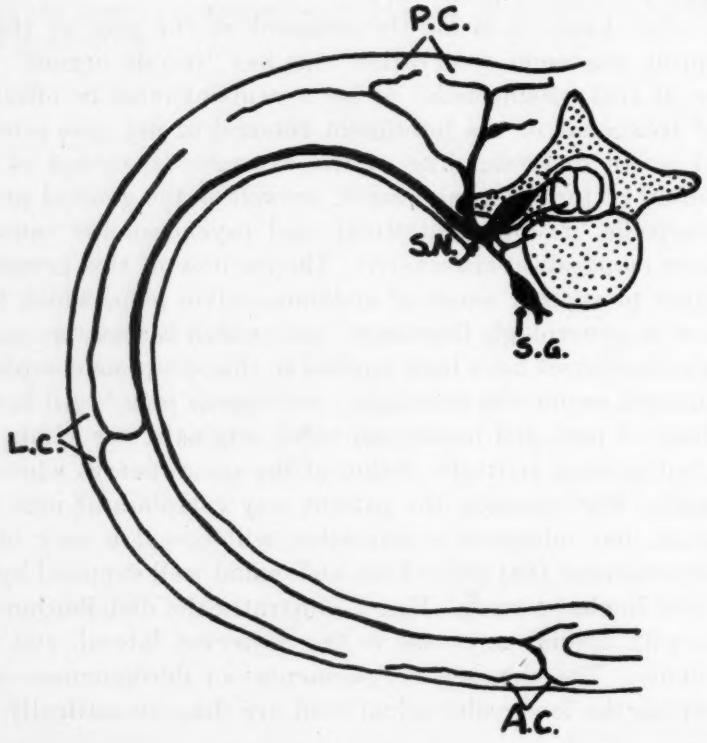

Fig. 1.—Distribution of lumbar spinal nerve. S.N.—spinal nerve, S.G.—sympathetic ganglion, P.C.—posterior cutaneous branch, L.C.—lateral cutaneous branch, A.C.—anterior cutaneous branch.

There is nothing particularly characteristic in the history except the absence in many cases of any symptoms referable to the back or spine. Occasionally there may be a history of recent respiratory infection or slight trauma. Frequently the pain is aggravated at the time of menstruation, which serves only to confuse the picture.

On examination, after localizing the pain, one then attempts to demonstrate the presence of abdominal wall tenderness over the area of distribution of the corresponding spinal nerves. This tenderness, though diffuse, is not uniform, but usually more pronounced over the areas where cutaneous branches of the nerve perforate the deeper structures and become more superficial. One will find tenderness to pinching if the subcutaneous fat is compressed between the fingers (Fig. 3), or there will be tenderness to firm finger pressure against the tensed abdominal wall (Fig. 4). In this connection, one will often find that the more the patient tenses the abdominal wall and pushes the finger away from underlying organs, the more severe is the tenderness. The opposite side is used as a control; rarely are somatic pain and tenderness bilateral, at least

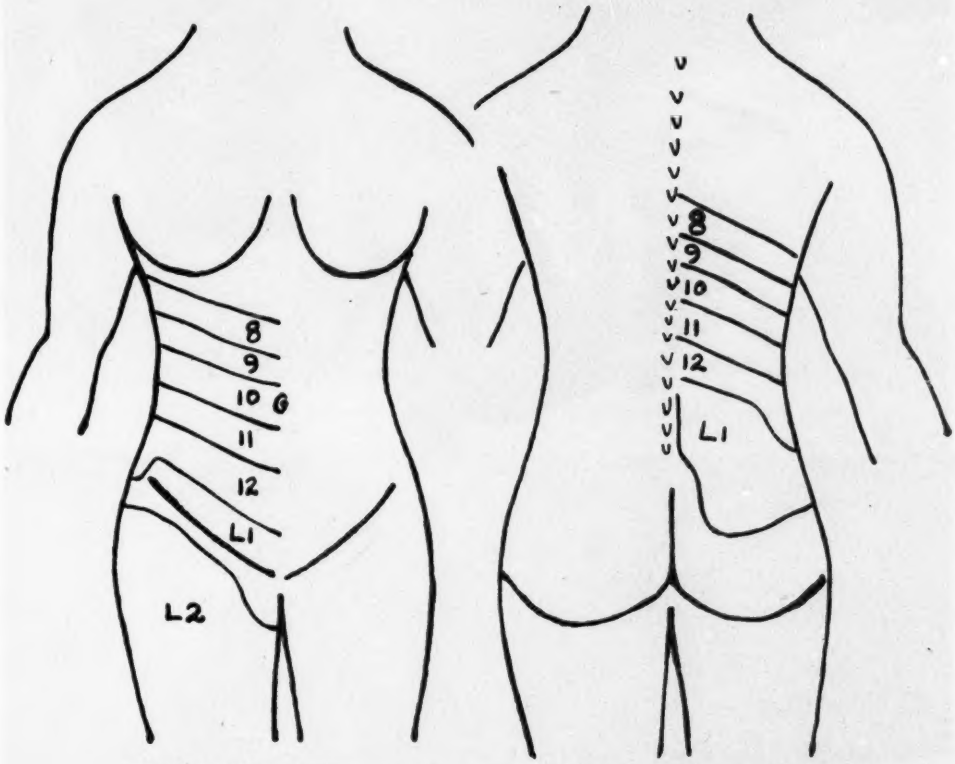

Fig. 2.—Dermatomes of the lower abdominal wall and back.

at the same level. Areas of tenderness in the paravertebral region are frequently found, at levels which correspond to the tender anterior distribution (Fig. 5). Obviously, this diffuse tenderness will not be discovered if only the site of subjective pain is palpated. When tenderness is limited to the distribution of one or more dermatomes, it is defined as segmental tenderness. With associated persistence of pain within these tender segments, a diagnosis of segmental neuralgia or somatic pain can be made.

The diagnosis is confirmed by paravertebral procaine block of the nerve trunks supplying the tender segments, whereupon the pain and tenderness disappear. The technique of paravertebral block of the spinal nerve root—which

must not be confused with paravertebral sympathetic block—is adequately described by Judovich and Bates,[2] whose text contains an excellent and complete exposition of this entire subject.

In this series, 2 per cent procaine was used for the initial diagnostic block, and, in most cases, subsequent blocking solutions contained procaine and Dolamin, the latter developed by Judovich and Bates, the active principle of which is ammonium sulfate. This agent has been found to inhibit the C fibers of the sensory nerves, and does not produce systemic effects, or change in skin sensation or motor function. It seems to be the ideal longer-acting agent for therapeutic nerve block.[6]

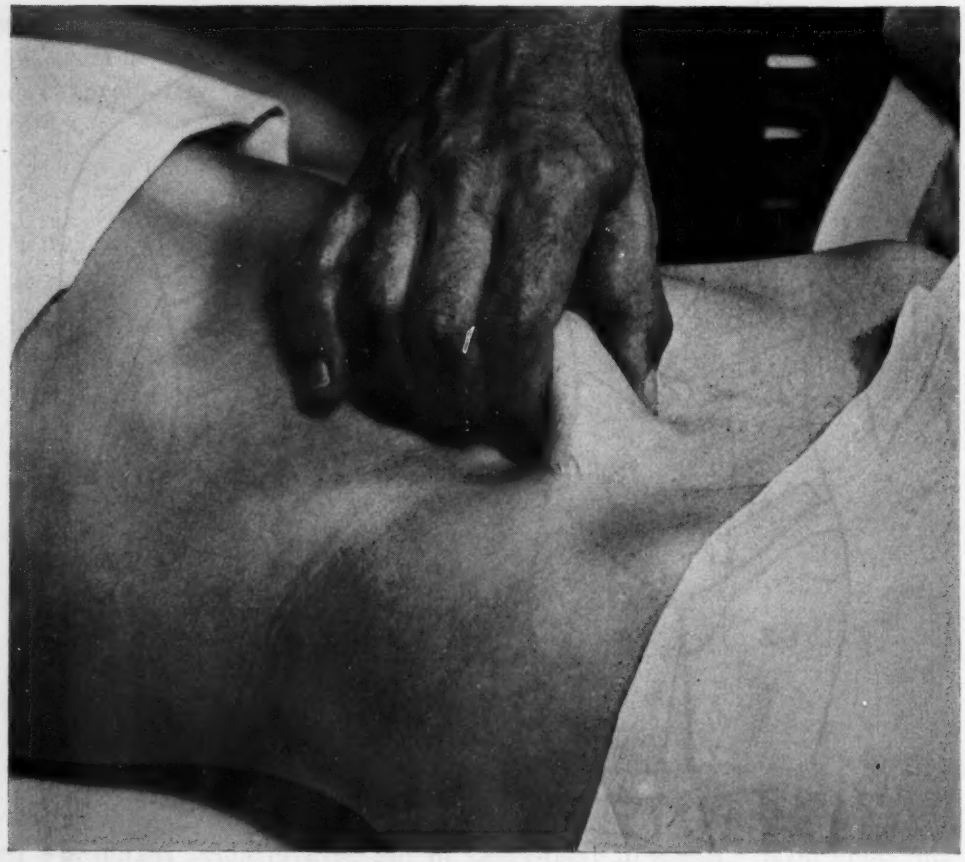

Fig. 3.—Eliciting pinch tenderness of the abdominal wall.

Table I represents the findings and treatment in twenty-three cases in which a diagnosis of somatic abdominopelvic pain was made. Surgical procedures shown in parentheses were performed prior to the onset of somatic pain, and have no bearing on the present complaints. It is of extreme interest to note, however, that nine of these twenty-three patients had fourteen major operations, in ill-advised attempts to relieve their somatic pain, without improvement.

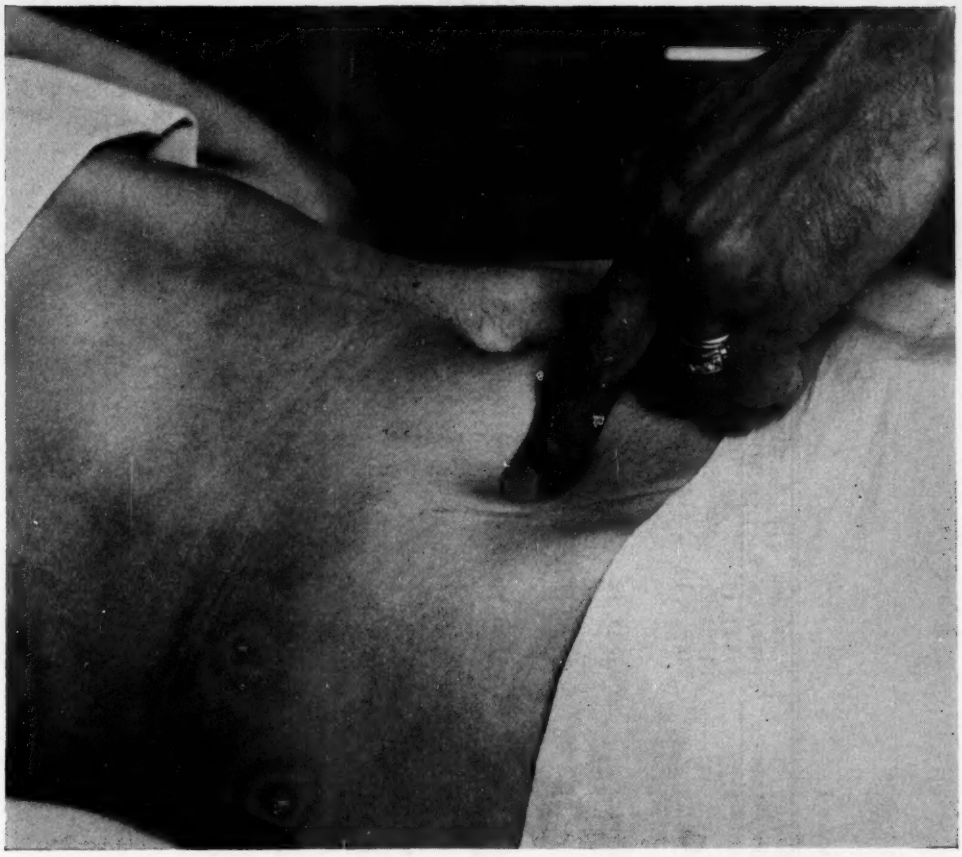

Fig. 4.—Eliciting pressure tenderness of the tensed abdominal wall.

Fig. 5.—Eliciting paravertebral tenderness.

TABLE I

	PAIN	PREVIOUS SURGERY	OTHER STUDIES	TENDER SEGMENTS	NERVE BLOCKS*	RESULT
H. F.	LLQ, 3 weeks	(Appendectomy)		D-11, 12 L-1	P 3/31/48	No recurrence 40 months
M. P.	LLQ, back, 2 years	Total hysterectomy, bilateral salpingo-oophorectomy. No improvement		D-8, 9, 10	P 9/21/48	No recurrence 14 months
B. H.	RLQ, back, 4 years		Culdoscopy	D-11, 12	P 9/28/48 DP 10/ 8/48	No recurrence 34 months
F. D.	RLQ, back, 3 years	Appendectomy. No improvement		D-10, 11, 12	P 10/ 4/48 DP 10/12/48	Relief right lower quadrant pain, no relief backache
F. Da.	RLQ, 4 months		Cholecystogram	D-10, 11, 12	P 6/14/49	No recurrence 25 months
I. G.	RLQ, menstrual exacerbation, 2 years	Right salpingo-oophorectomy Right salpingo-oophorectomy. No improvement	X-ray spine (scoliosis)	D-12 L-1, 2	P 6/29/49 DP 7/ 6/49 DP 7/11/49	Slight menstrual pain 9 months
M. B.	RLQ, back, 3 years	(Appendectomy)	X-ray stomach. Cholecystogram Pyelogram	D-9, 10, 11	P 7/ 2/49 DP 7/ 5/49 DP 7/11/49	No recurrence 24 months
L. S.	RLQ, right flank, 2 years	(Right salpingo-oophorectomy)		D-10, 11, 12	P 9/13/49 DP 9/16/49	No recurrence 17 months
H. J.	LLQ, 2 years			D-11, 12 L-1	P 3/28/50	No recurrence 12 months
F. F.	RLQ, back, 3 weeks	(Appendectomy, right salphingo-oophorectomy)	Culdoscopy	D-12 L-1, 2	P 4/24/50 DP 4/29/50	No recurrence 15 months
A. W.	RLQ, 5 years	Appendectomy. No improvement		D-11, 12 L-1	P 5/10/50	No recurrence 8 months
J. W.	RLQ, 3 years			D-11, 12 L-1	P 3/ 7/51	No recurrence 4 months

M. R.	RLQ, anterior thigh, buttock	Laminectomy. No improvement	Cystoscopy (Urethritis)	D-12 L-1, 2	P 3/24/51 DP 3/27/51	Relief except suprapubic 4 months
F. M.	RLQ, 3 years	(Appendectomy)		D-11, 12	P 4/20/51 DP 4/23/51	No recurrence 3 months
M. T.	RLQ, 16 years	Appendectomy, right oophorectomy, right hernia. No improvement	Pyelogram	D-11, 12 L-1	P 5/ 4/51 DP 5/ 8/51	Relief "first time in years." No recurrence to date
R. W.	RLQ, 5 months	Appendectomy. No improvement	Pyelogram	D-11, 12 L-1	P 5/ 9/51 DP 5/11/51	No recurrence to date
G. H.	RLQ, back, 2 months	(Appendectomy)	X-ray spine. Pyelogram	D-10, 11, 12	P 5/18/51 DP 5/22/51	No recurrence 2 months
N. G.	RLQ, right flank, costovertebral angle 8 years	Appendectomy. Cholecystectomy. Hysterectomy. Ureteral dilatations. 2 months. No improvement	X-ray spine. Pyelogram	D-10, 11, 12	P 7/21/51 DP 7/25/51	No recurrence to date
Z. C.	LLQ, 4 years	Left salpingectomy. No improvement		D-10, 11, 12	DP 10/ 8/48 DP 70/18/48	Recurrence 7 months later (pregnant), subsided spontaneously after 10 days
R. P.	RLQ, back, 1 year			D-10, 11, 12	DP 10/19/48 DP 11/27/48	Recurrence 4 weeks later. No recurrence 4 months
C. B.	LLQ, anterior thigh			L-1, 2	P 3/ 3/49 P 3/ 7/49 DP 5/31/49	Recurrence 7 weeks later. No recurrence
E. H.	RLQ, LLQ, 5 years	(Appendectomy)	Cystoscopy	D-12, L-1 Bilateral	P 2/15/50 Bilateral	No relief. Hysterectomy (fibroid) 4/12/50
L. H.	RLQ, 3 years	(Right nephrectomy)	X-ray stomach. Cholecystogram Cystoscopy	D-12 L-1	P 10/15/50 DP 10/19/50 DP 10/24/50	No relief. Repeat cystoscope, right pyoureter removed. Cured

*P represents procaine alone.
DP represents Dolamin and procaine.

Other diagnostic studies, all negative except as listed otherwise, were done principally to document this presentation. However, the clinical diagnosis of this syndrome is simple and definite enough in most cases perhaps to warrant an initial diagnostic nerve block prior to more expensive investigative procedures. The segmental distribution of tenderness and number and type of nerve blocks is shown. "P" represents procaine alone. "DP" indicates Dolamin and procaine.

Eighteen of the twenty-three patients were relieved of their pain without recurrence in the intervals shown. Three patients suffered recurrence of their pain; one for a short interval with spontaneous remission, two required additional therapeutic block, have been free of pain since. In two patients, no relief of pain was experienced; these cases are listed as failures.

Comment

It should be emphasized that rest in bed for a week or ten days nearly always results in temporary relief of somatic pain. The patient for a while is better after the hospitalization and bed rest incident to the removal of some organ.

But when after a time the pain returns with all its former severity, the patient is likely not to return to the surgeon, who continues in the assurance that her troubles have been cured. Two of these patients, after unsuccessful operations, received manipulative treatment at the hands of an osteopath and a chiropractor, respectively. As one might guess from the nature of their illness, they experienced more lasting benefit from this than from the surgery.

There is nothing new about this syndrome of somatic pain. It is rather so old that perhaps it has been forgotten by many of us in our preoccupation with visceral disease. The experience with this small series of patients, so many of whom had been subjected to futile surgical procedures, would seem to warrant the re-emphasis of this concept to all who profess to treat abdominopelvic pain. Apparently it is not a platitude to point out that "pain in a given area does not of necessity mean pain in a viscus,"[3] and that recovery from surgery does not of necessity mean cure of a disease.

Summary

The clinical diagnosis of somatic abdominopelvic pain—as distinguished from pain due to visceral disease—is described. Twenty-three patients were treated by paravertebral nerve-root block, using a solution of procaine and Dolamin, according to the method of Judovich and Bates. Twenty-one patients were relieved of their pain; nine of these patients had previously been subjected to surgery without benefit.

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Discussion

DR. R. L. HAAS, Ann Arbor, Mich.—The implication in Dr. Eller's paper that not every painful abdomen or pelvis requires opening is a timely one, and one which cannot be overemphasized.

The evaluation of the relief obtained in any painful affliction by the application of any method of treatment is at best a difficult task due to the marked individual variation in response to painful stimuli. When confronted by a patient complaining of pain in the abdominopelvic area, one must of course always keep in mind the possibility of a functional or psychic element. Frequently the assistance of a competent psychiatrist is of great value. One wonders what part, if any, emotional factors played in the cause of the pain, and in the relief obtained in Dr. Eller's patients.

I have heard it said by competent general surgeons—and my experience tends to support it—that patients who have had appendectomies will occasionally have ill-defined discomfort in the region of the scar for years. The origin of this pain is not clear. A large proportion will be relieved permanently after subcutaneous infiltration about the scar with a local anesthetic agent. This might suggest improper nerve regeneration in the incision area, another possible cause of abdominopelvic somatic pain.

I should like to ask Dr. Eller whether he has tried the intracutaneous injection of local anesthetic agents in cases of the type he describes, and whether he would expect any benefit from so doing.

I should like to also ask Dr. Eller what thoughts he has concerning the explanation for the permanent relief obtained after paravertebral block. He has stated that there are many underlying causes for the nerve-trunk irritation including infection, and postural, traumatic, and arthritic conditions. Are we to assume that a paravertebral block will result in a correction of these abnormalities?

I think we are indebted to Dr. Eller for reminding us again of the futility of operating to look for pain, and the necessity for keeping in mind the multitude of possible causes for pain in the abdominopelvic area.

DR. ALBERT HIRSHEIMER, Dayton, Ohio.—I was very happy indeed to have Dr. Eller bring this matter to our attention. I have been interested in it for a long time, and I think that, since there is generally a certain amount of skepticism as to its reality, a note as to its incidence might be useful.

I observed, without any reference to the patient's complaints, a consecutive series of 674 patients, about equally divided between pregnant and nonpregnant women, looking for the objective signs of segmental tenderness. The incidence of segmental tenderness in these patients was 27.9 per cent, about equally divided between the nonpregnant and the pregnant women.

In slightly less than half of these women, or 13.2 per cent in the pregnant and 11.8 per cent in the nonpregnant, there was some apparent relationship between complaints that the patient had and the presence of peripheral tenderness.

Dr. Hass mentioned the possible relationship of this syndrome to the patient's emotional status. As a casual, incomplete observation of the patient's emotional status, I judged that of these patients there were some who had what may be roughly described as a tension state. Of the whole group of patients with segmental tenderness, 42 per cent with subjective pain had a tension state, whereas of those without any complaints referable to the objective findings, 27 per cent had a tension state.

There also was found in these patients the presence frequently of tenderness and spasm of the perineal and presacral muscles, a state which is often associated with low back pain and pelvic complaints. The incidence was rather high in the patients who complained

of pain and were found to have segmental tenderness—62 per cent. On the other hand, it was also found in 37 per cent of those who had segmental tenderness without symptoms associated with it.

DR. ELLER (Closing).—There seem to be three main points brought out by the discussors: First, the inference of the psychosomatic impact on symptoms and results of treatment. I have wondered about that considerably in this as in other instances, as have we all.

I wonder if perhaps we do not tend to fall into the error of diagnosing psychosomatic disease by exclusion rather than by its direct and positive signs, in that if we cannot find something else to call it, we call it psychosomatic.

Second, if, in this particular connection, psychosomatic pain which has been of months' to years' duration can be arrested by the infiltration of a few nerve trunks with a local evanescent injection, then we have quite by accident stumbled upon an unsuspectedly potent psychotherapeutic weapon.

As to subcutaneous Novocain infiltration, I have had no experience with that except in the few cases in labor, when I found no effect, good, bad, or indifferent.

Why the permanent relief? I don't think we should use that term; but why long-lasting relief? Men of the caliber of Carnett and Thomas and Judovich and Forrester have debated that and have written pages on it. It does not appear to me that they know the answer, and I don't know the answer either.

USE OF PROTAMINE SULFATE AND TOLUIDINE BLUE FOR ABNORMAL UTERINE BLEEDING*†

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THE proposed causes for idiopathic vaginal bleeding in obstetric and gynecologic patients are legion. In the past, attention has been brought to the importance of irregular shedding of the endometrium,[1] hormonal disturbances,[2] emotional upsets,[3] as well as other proposed factors[4, 5] which may contribute to etiology. Likewise, the management of idiopathic vaginal bleeding varies considerably. It may consist of the simple administration of thyroid or one of the other hormonal preparations in any of their many forms, it may be more complex, necessitating curettage, or so extreme as to render the uterus functionless by the use of x-ray or radium or even extirpation of the organ itself.

Recently, Allen and associates[6] reported the presence of an inhibitor to blood clotting during certain hemorrhagic conditions. This undefined inhibitor was neutralized (in vitro and in vivo) by protamine sulfate and toluidine blue. According to Allen and his co-workers,[7] its presence can be determined titrametrically. Variations occur in this titration during different physiologic and pathologic conditions associated with bleeding episodes. Attempts to show that the protamine titration is only another manifestation of an altered platelet level have not been conclusive,[8] as the protamine titration may be normal in the presence of a low or absent platelet count and, correspondingly, may be elevated when the platelet count and prothrombin time are normal. The fact that the protamine titration can be increased when large amounts of heparin or heparin-like substances are present does not mean that the principal factors are these substances, as other endogenous compounds not of the heparin family will produce an elevated protamine titration and be neutralized by protamine sulfate or toluidine blue. Abnormal values in protamine titration should be interpreted in respect to all of the known clotting factors.

Considering the varied and oftentimes radical therapeutic measures employed in cases of abnormal uterine bleeding, our interest centered on the possible use of protamine sulfate and toluidine blue in these cases. It has been stated that a large percentage of patients with abnormal uterine bleeding and without demonstrable pelvic pathology have elevated protamine titrations.[9]

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According to this source, the bleeding improves in a majority of cases following the administration of protamine sulfate or toluidine blue. Accordingly, a study was undertaken to evaluate further the use of these substances in bleeding obstetric and gynecologic patients.

Material and Method

Patients were obtained from the hospital services of the Department of Obstetrics and Gynecology of the University of Nebraska College of Medicine. A group of normal menstruating and nonmenstruating women were chosen as controls from the personnel of the University Hospital.

The technique of titration was described by Allen and collaborators.[7] Eleven c.c. of venous blood are drawn with a large-gauge needle. This blood is immediately placed in a standard graduated centrifuge tube containing 0.1 c.c. of liquid commercial heparin. The blood and the heparin are thoroughly mixed by slowly inverting the tube twelve to fifteen times. Exactly 1 c.c. of this blood is accurately pipetted into each of six Wassermann tubes containing measured amounts of protamine sulfate, increasing from 0.1 mg. in the first tube to 0.2 mg. in the sixth tube. Each tube is briskly shaken eight to ten times and allowed to stand undisturbed for one hour. The end point is determined by the least amount of protamine required for clot formation in one hour. The normal titration was established at 0.12 mg. of protamine sulfate. The controls consisted of a number of normal males and females, and each new solution of protamine sulfate was checked with these controls before it was used for testing.

TABLE I. DATA ON PATIENTS STUDIED. ONE HUNDRED EIGHTY-TWO TITRATIONS ON ONE HUNDRED EIGHT PATIENTS

DIAGNOSIS	TOTAL NUMBER OF PROTAMINE TITRATIONS	TOTAL NUMBER OF PATIENTS	FIRST PROTAMINE TITRATION ON EACH PATIENT	
			NORMAL	INCREASED
Uterine Bleeding.—				
Normal female controls	24	8		
Menstruating			1	7
Between periods			8	
Menometrorrhagia	95	62	15	47
Postpartum hemorrhage	12	8	3	5
Abortion	2	2	2	
Carcinoma of the cervix	2	2	2	
Other Bleeding.—				
Postoperative hemorrhage	6	5	2	3
Epistaxis	5	5		5
Hemophilia	5	3	1	2
Gastrointestinal bleeding	7	2		2
Undiagnosed ecchymosis	4	2		2
Thrombocytopenic purpura	5	2		2
Chronic leukemia	5	1		1
Chronic nephritis	1	1	1	
Malignant melanoma	5	1		1
Absent platelets	1	1	1	
Patients on ACTH	3	3	1	2
Total	182	108		

In the group of patients treated in this study, one of three plans of treatment was followed. Five were treated with parenteral injections of protamine sulfate,* 50 mg. daily for four days. One patient was given intravenous toluidine blue† using 150 c.c. of 0.1 per cent solution twice daily for three days and

*Eli Lilly and Company.
†Abbott Laboratories.

150 c.c. once daily for three days. The majority of patients (17) were given oral toluidine blue* in 100 mg. capsules, using one capsule twice daily for four days. After four days of treatment, the protamine titration was rechecked and, if it had not returned to normal, the treatment was continued for two additional days. In two cases both protamine sulfate and oral toluidine blue were given. No serious untoward reactions were encountered and only two of the patients on oral toluidine blue experienced moderate gastric distress. All on toluidine blue had discolored urine, but no other symptoms.

Results

A total of 182 protamine titrations were done on 108 patients. At the time of the menstrual period, a majority of the normal women tested had a slight to moderate increase in their protamine titration, usually increasing to 0.14 mg. and rarely to 0.16 mg. There was no intermenstrual alteration from a normal of 0.12 mg. A complete blood study was obtained on each of these controls, including the bleeding time, clotting time, prothrombin time, and platelet count. None of these had a significant alteration from the normal. The controls were studied monthly for three months.

TABLE II. RESULTS OF TREATMENT IN CASES OF MENOMETRORRHAGIA AND POSTPARTUM HEMORRHAGE BY PROTAMINE SULFATE OR TOLUIDINE BLUE

DIAGNOSIS	TOTAL NUMBER OF PATIENTS USED	PROTAMINE TITRATION		RESULTS		
		INCREASED BEFORE	DECREASED AFTER	BLEEDING STOPPED	BLEEDING LESSENED	NO EFFECT
Menometrorrhagia	25	23	25	12	7	4
Postpartum hemorrhage	5	5	5	4		1

TABLE III. RESULTS NOTED IN PATIENTS WITH MENOMETRORRHAGIA BUT TREATED BY OTHER METHODS

TREATMENT USED	MENOMETRORRHAGIA WITH AN INCREASED PROTAMINE TITRATION		MENOMETRORRHAGIA WITH A NORMAL PROTAMINE TITRATION	
Total patients studied	24		15	
Observation only	10		6	
Continued bleeding		8		5
Bleeding stopped		2		1
Curettage	9		4	
Continued bleeding		6		3
Bleeding stopped		3		1
Hysterectomy		2		3
Hormone therapy	3		2	
Bleeding stopped		1		1
Symptoms recurred		2		1
Pregnancy	2		1	
Normal pregnancy		1		1
Late abortion, 4 months		1		
Total patients with continued symptoms	14		6	

Of 62 patients who had abnormal uterine bleeding and who showed no pelvic pathology, 47 (75 per cent) had an elevation in protamine titration (Table I). Approximately one-half of the patients with elevated titrations were treated with protamine sulfate or toluidine blue (Table II) while the remaining group were followed without treatment or with treatment by other means for comparison. All but 4 of the treated patients reported improvement and a majority of these experienced complete relief of symptoms for

*Abbott Laboratories.

varying periods of time (Table II). All patients had a return of their titrations to normal on protamine sulfate or toluidine blue regardless of the clinical response. The group of untreated controls showed a much less encouraging result since very few of them had spontaneous relief of symptoms and the greater number continued to have bleeding necessitating further procedure (Table III). Nine patients were treated with curettage, and 2 of these required a hysterectomy later. Three were treated with ovarian hormones and showed a temporary response, but 2 had recurrences of their previous symptoms with some increase in severity. Two patients became pregnant, and experienced no abnormality with their pregnancies. A smaller group of patients who had normal protamine titrations were likewise followed and showed approximately the same percentage of spontaneous remission of symptoms and followed the same clinical courses as did the untreated controls. Two of the group with normal titrations were given protamine sulfate empirically and no response was noted. A hematologic study was done on all of these patients.

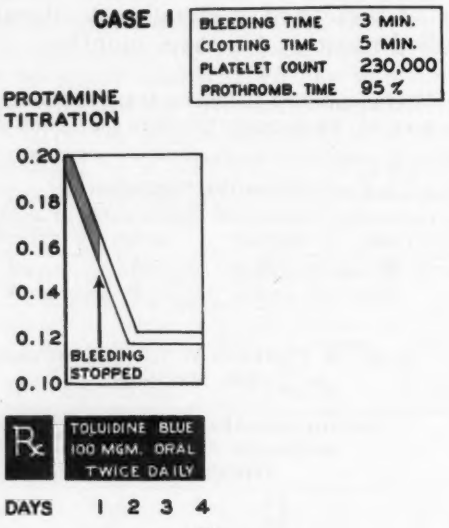

Fig. 1.

In order to illustrate the use of the protamine sulfate and toluidine blue, the following cases are presented:

CASE 1.—Miss J. N., aged 24 years, para 0, gravida 0, was first seen in January of 1951 with a complaint of excessive vaginal bleeding of three days' duration commencing on the third day of the menses. Previous menstrual periods had been entirely normal. Past history revealed an appendectomy and right cyst-oophorectomy three years previously. General physical examination was noncontributory. Pelvic examination disclosed a nulliparous outlet, cervix closed, uterus anterior and of normal size, shape, consistency, and mobility. The adnexa were not enlarged. Hematologic studied were: bleeding time, three minutes; clotting time, five minutes; prothrombin time, 95 per cent; platelet count, 230,000; all within normal limits. The protamine titration was 0.20 mg. Toluidine blue 100 mg. twice daily by mouth was administered for four days. The vaginal bleeding stopped after the first day of treatment and subsequent menses have been entirely normal. The events in the case are reported graphically in Fig. 1.

CASE 2.—Mrs. M. M., aged 26 years, para ii, gravida ii, was first seen in October of 1950 with complaints of daily vaginal spotting of six weeks' duration. An entire gamut of treatment was tried, including hormone therapy and two curettements with no relief. Past

history was noncontributory with normal regular menses since their onset and two uneventful pregnancies. General physical examination was nonrevealing. Pelvic examination disclosed a parous outlet, cervix firm, uterus anterior and of normal size, shape, consistency, and mobility. The adnexa were not enlarged. Hematologic studies were: bleeding time, six minutes; clotting time, three and one-half minutes; prothrombin time 100 per cent; platelet count, 116,000; all within normal limits. The protamine titration was 0.14 mg. Protamine sulfate 50 mg. daily was given intramuscularly for four days. The vaginal bleeding stopped after the second day of treatment and subsequent menses have been entirely normal. The events in this case are portrayed graphically in Fig. 2.

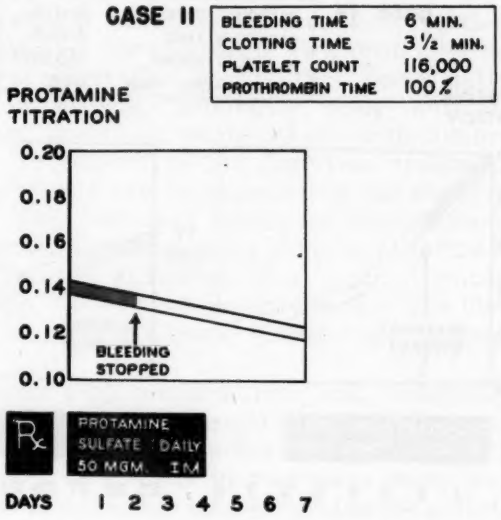

Fig. 2.

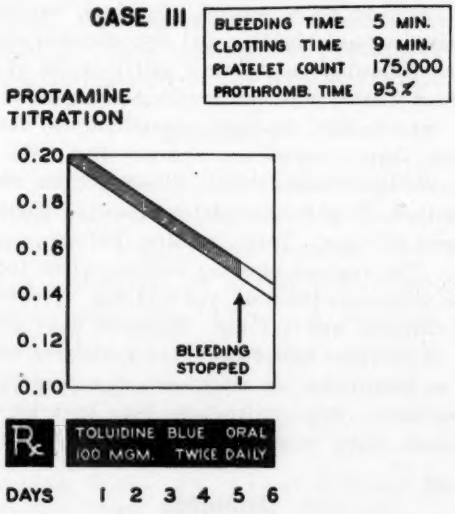

Fig. 3.

Case 3.—Mrs. L. B., aged 27 years, para ii, gravida ii, was first seen in December of 1950 with complaints of excessive vaginal bleeding of three months' duration and fatigue of two months' duration. The patient was given thyroid and a trial of pessary neither of which relieved her symptoms. Past history disclosed an appendectomy and right cyst-oophorectomy two years previously. General physical examination was noncontributory. Pelvic examination

revealed a parous introitus, cervix moderately eroded, uterus retroverted and retroflexed, otherwise normal in size, shape, consistency, and mobility. The adnexa were normal bilaterally. In January, 1951, hematologic studies were: bleeding time, five minutes; clotting time, nine minutes; prothrombin time, 95 per cent; platelet count, 175,000; all within normal limits. The protamine titration was 0.20 mg. Toluidine blue, 100 mg. twice daily by mouth, was administered for six days. The vaginal bleeding stopped after the fifth day of treatment when a repeat titration was 0.14 mg. Treatment was continued as above for the additional day and subsequent menses have been normal. The events in this case are portrayed graphically in Fig. 3.

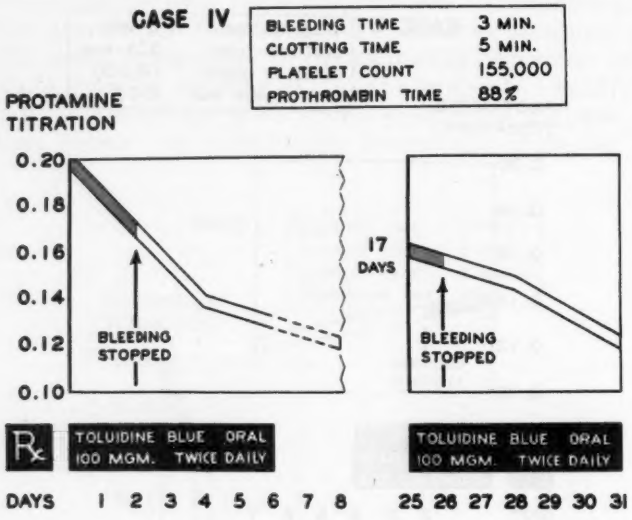

Fig. 4.

CASE 4.—Miss J. H., aged 23 years, para 0, gravida 0, was first seen in August of 1950 with complaints of excessive vaginal bleeding and hypochromic anemia of six months' duration. Symptoms continued following curettement and in spite of attempted treatment with thyroid and estrogens. Past history was nonrevealing and general physical examination was noncontributory. Pelvic examination disclosed a nulliparous outlet, cervix eroded, uterus anterior and of normal size, shape, consistency, and mobility. The adnexa were not enlarged. In February of 1951, hematologic studies were: bleeding time, three minutes; clotting time, five minutes; prothrombin time, 88 per cent; platelet count, 155,000; all within normal limits. The protamine titration was 0.20 mg. Toluidine blue, 100 mg., was administered twice daily by mouth for four days. The vaginal bleeding stopped after the second day of treatment and on the fourth day the protamine titration was 0.14 mg. Treatment was continued for two more days and a recheck titration was 0.12 mg. Eighteen days after the bleeding ceased the patient had a recurrence of previous symptoms. The protamine titration was again 0.16 mg. Treatment was repeated as before for six additional days and all vaginal bleeding stopped after the first day of treatment. Repeat titrations have been normal since the second treatment and subsequent menses have been normal. The events in this case are portrayed graphically in Fig. 4.

Comment

The results of this study, to a large extent, parallel the findings of Allen.[6] This was true in respect to the moderate elevation of titration during normal menses as well as the high percentage of increased values in that group of patients with abnormal uterine bleeding. We did not find, however, an increased clotting time in the majority of patients with elevated titrations, as observed by others. In reviewing this series of cases, it was found that the

results of treatment with protamine sulfate and toluidine blue varied directly with the duration of symptoms. Patients with prolonged bleeding histories required longer series of treatments or repeated courses of treatment before amelioration of symptoms occurred, while those with a shorter duration of bleeding were often cured or markedly improved with one course of treatment of toluidine blue. In contrast to results given in another report,[9] toluidine blue proved just as effective orally as intravenously. The patients experienced both relief of symptoms and a return of the protamine titration to normal. No correlation could be made between the degree of elevation of the titration and the clinical response to treatment.

Some comment should be made on the interpretation of the protamine titration and the indication for treatment with protamine sulfate and toluidine blue. It is apparent from the results that some patients have elevated titrations with normal menses. Similarily, some individuals with abnormal bleeding have normal titrations while others with abnormal bleeding show elevated titrations. In respect to the first two, treatment is not indicated, whereas satisfactory results can be expected in the great majority of patients in the third group. This point can hardly be overemphasized since misuse of the method can occur if all patients with abnormal uterine bleeding are treated with protamine sulfate or toluidine blue without consideration for their titrations. In addition, the correct identification of the bleeding defect should be established by obtaining complete hematologic studies before therapy is instituted.

Although treatment with toluidine blue and protamine sulfate may apply only to certain specific types of abnormal bleeding, its use in gynecology seems warranted. So often treatment by other means is either unsatisfactory, prolonged, or radical, that new ideas in treatment seem well justified. As an expense item, the use of toluidine blue or protamine sulfate seems well worth a trial. In the second case reviewed, a hysterectomy was considered because of the persistence of symptoms but, fortunately, a protamine titration was obtained and the patient was successfully treated with protamine sulfate. Finally, the method used for determining the protamine titration is relatively easy and well within the limitations of the average clinical laboratory.

Summary

The protamine titration was slightly elevated in women experiencing normal menstrual periods and more increased in 75.8 per cent of women with abnormal vaginal bleeding. Eighty per cent of the treated patients with elevated titrations were improved or cured following the administration of protamine sulfate and/or toluidine blue. A control group with elevated titrations, treated by other means, did not fare as well. Patients with longer bleeding histories required longer courses of treatment.

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Discussion

DR. HAROLD PRIDDLE, Detroit, Mich.—We also have been particularly interested in the use of these two drugs in hypermenorrhea, postpartum hemorrhage, and postoperative bleeding. As the authors have shown, we also have had a large number of patients respond either to toluidine blue or to protamine sulfate if they have abnormal protamine titrations. We also have done a little work on the effects of protamine on the sedimentation rate, but at the present time we have little material to report.

The program that the authors outline is in agreement with most programs using these two drugs, except that occasionally we find that 200 mg. or even 300 mg. of toluidine blue by mouth is not enough to bring about a response in some cases of hypermenorrhea and to decrease the titration to normal. We have two patients at the present time who required 400 mg. of toluidine blue per day. They got a little nausea with this dose, as the authors mentioned, but they preferred the nausea to the profuse vaginal bleeding.

As to protamine, occasionally it will take three 50 mg. ampules a day to bring about the response you desire. Fifty mg. are occasionally given intravenously, particularly in cases of postpartum hemorrhage, if the titration is abnormal.

Occasionally we give these patients their toluidine capsules to keep at home, once we have corrected their titrations. If perchance four, five, or six months later they have a repeated episode of hypermenorrhea they may take the capsule and thus occasionally prevent hospitalization for severe anemia.

A little caution about intravenous toluidine blue: When you give it intravenously you should take precautions to prevent extravasation, because the patient will have a cellulitis and possibly a slough if there is any extravasation. Also, it should be given very slowly. The authors gave 100 mg. intravenously. We prefer giving 300 mg. in 1,000 c.c. of normal saline, and letting it drip as slowly as possible for 8 to 10 hours, which is a long period of time, to be sure, for the patient to lie in a recumbent position, but by this method we get a prolonged action of the drug.

Each one of these drugs which the authors have mentioned works very well. Protamine is more rapid in its action, but does not last as long, while toluidine blue, being a little slower in its action, will give an effect for a longer period of time.

The only criticism I have of the authors' paper is doing only 182 titrations in 108 patients. We prefer to do a minimum of two titrations on any individual, even normal controls. A normal should be taken at about the time of ovulation, at least we have found that that gives you a more normal figure; and, of course, if she has hypermenorrhea you should do a titration at the menstrual period and also during the time of the therapy. We feel that two is a minimum number of titrations that each patient should have. Of course, you prefer more during the time of therapy.

One must not become discouraged in the treatment of a patient with hypermenorrhea using toluidine blue or protamine. Sometimes it will take two or three menstrual periods of therapy with toluidine blue by mouth or protamine intramuscularly to give the response you desire. The titration may be essentially normal, but the patient is still having abnormal menstrual periods, and we consider she has not returned to normal until her menses are as they were before the episode of hypermenorrhea.

The 0.14 mg. of protamine sulfate titration is a working basis for abnormality, but if a patient is having abnormal bleeding and there is no other gynecological reason for it, and even if she does not show an abnormal protamine titration, we feel that the patient should

be given either protamine or toluidine blue empirically, for many times there will be a response. However, just as often there will be no response to this therapy. This is not to be used empirically in all cases of hypermenorrhea; the patient should have a complete gynecological work-up. Thus this is not a substitute for a complete gynecologic study.

You may think that protamine titration is an institutional procedure, but I assure you that anyone can learn how to do a protamine sulfate titration. The technician in your office or in the office building in which you practice can learn to do this titration very quickly; and, as it takes only one hour, you can have your results in your office in a very short period of time.

If the patient has an abnormal titration you can begin your therapy with oral toluidine blue. Many of these patients have shopped among a large number of physicians, and if you can correct the menorrhagia she will be most grateful. It is not something that has to be done in a teaching institution or a large hospital. It can be done in any ordinary laboratory.

The authors showed two patients who had carcinoma with normal titrations. The only two patients with cervical carcinoma I have had contacts with had abnormal titrations.

Last, the authors did not mention pregnant patients. There will be abnormal protamine titrations in a large number of pregnant patients, but these same patients will have normal deliveries, no postpartum hemorrhage, and slowly their titrations will return to normal in approximately ten days after delivery.

The thing I wish to re-emphasize about the use of toluidine blue and protamine sulfate is that the presence of an increased titration of protamine sulfate, per se, does not mean that that patient will bleed; but if the patient has abnormal bleeding, and has an increased titration then this is another method of treating her. Many such patients will respond.

EXPERIENCE WITH PRANONE AND ACTH IN Rh-SENSITIZED PREGNANCIES*†

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(From the Department of Obstetrics and Gynecology, University of Utah College of Medicine)

SINCE it was first demonstrated that Rh incompatibility was responsible for some previously unexplainable stillbirths and neonatal deaths, attempts have been made to prevent these fetal disasters in three ways:

1. Interruption of the pregnancy when there was suspicion that the infant was being involved by hemolytic disease, evidence for this suspicion being chiefly the demonstration of a rising antibody titer in the mother's blood.

2. Treatment of the involved infant following delivery by single or exchange transfusions.

3. Treatment of the sensitized mother during pregnancy in an attempt to desensitize her.

All obstetricians who have tried the first method have found that merely interrupting the pregnancy (whether it be by cesarean section or induction of labor) cannot be expected to benefit the infant unless this is combined with treatment of the infant after delivery. When an infant survives such a combination of treatment, it is always difficult to assess the part played by interruption of the pregnancy in the end result. The consensus now seems to be that cesarean section or induction of labor, in themselves, can be expected to do little for the infant involved by hemolytic disease.

Although in most instances a rising antibody titer in the maternal blood means that the infant is involved by hemolytic disease, this is not always the case. We, like others, have had the embarrassing experience of having induced labor because of a rising maternal antibody titer, and then have been chagrined to find that the infant was either Rh negative or even Rh positive with minimal signs of hemolytic disease. Although apparently the generalization can be made that whenever albumin agglutinins are present in the maternal serum, they will invariably pass over into the fetal circulation, the level of the maternal antibody titer is a poor index of how severely the infant will be involved by hemolytic disease.

The third method for preventing fetal disasters from hemolytic disease due to Rh sensitization is the method with which we are concerned in this discussion. This aims at desensitizing the mother.

In January, 1950, Hoffman and Edwards, in the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, presented "A Preliminary Report on a New Con-

*Pranone for this study was furnished by the Schering Corporation; ACTH was furnished by the Armour Laboratories.

†Presented at the Nineteenth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Detroit, Mich., Sept. 20, 21, and 22, 1951.

cept in the Treatment of Rh-Negative Pregnant Women.'' The article reported on the results following administration of Pranone (anhydrohydroxyprogesterone) to Rh-negative women who were pregnant. The majority of the women who received the drug, although Rh negative, showed no evidence of sensitization, i.e., there were no antibodies present in the maternal blood. Only three patients showed the presence of antibodies. In each of these, the antibody titer fell following administration of Pranone and vitamin K. The fact that all the patients who started their pregnancies without antibodies failed to develop antibodies during their pregnancies is dubious evidence of Pranone's effectiveness, for we know that, without any treatment, only about 5 per cent of Rh-negative women will become sensitized, even though they are mated to Rh-positive men and are subjected to repeated pregnancies.

Material

In an attempt to confirm the observations of Hoffman and Edwards, we administered Pranone to a group of 35 pregnant patients who were sensitized to the Rh factor. The length of time during which the drug was administered and the daily dosage varied, but, in the majority of the patients, the drug was administered in a daily dose of at least 100 mg. over a period of at least 12 weeks. Several patients received 200 mg. of Pranone daily over a period of 25 weeks or more.

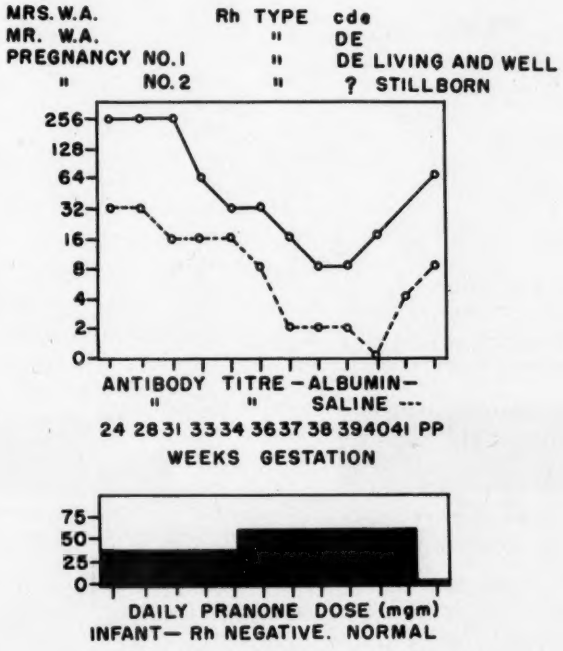

Fig. 1.

It has been well known for some time that the fetal prognosis in any Rh-sensitized patient depends chiefly on the history of the outcome of previous pregnancies. A sensitized Rh-negative patient who has previously lost an infant from hemolytic disease carries a much poorer prognosis than a patient who, although sensitized, has delivered a fetus involved by hemolytic disease

of a degree insufficient to cause fetal death. We find similar results in our patients when they are divided into two groups according to their past childbearing histories (Tables I and II).

TABLE I. OUTCOME OF PREGNANCIES AFTER ADMINISTRATION OF PRANONE TO NINETEEN RH SENSITIZED PREGNANT WOMEN WHO HAD NOT PREVIOUSLY LOST INFANTS FROM HEMOLYTIC DISEASE

Rh-negative infants	4
Stillborn infants	0
Neonatal deaths	2
Living and well	13
Total	19

TABLE II. OUTCOME OF PREGNANCIES AFTER ADMINISTRATION OF PRANONE TO SIXTEEN RH SENSITIZED PREGNANT WOMEN WHO HAD PREVIOUSLY LOST INFANTS FROM HEMOLYTIC DISEASE

Rh-negative infants	4
Stillborn infants	10
Neonatal deaths	1
Living and well	1
Total	16

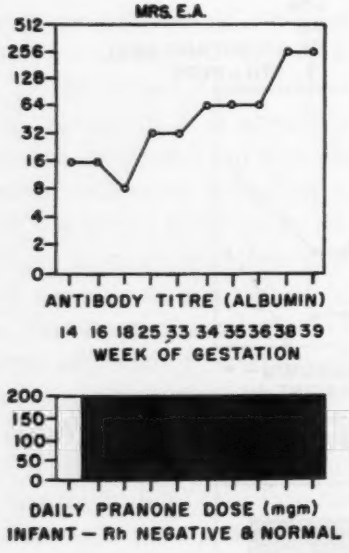

Fig. 2.

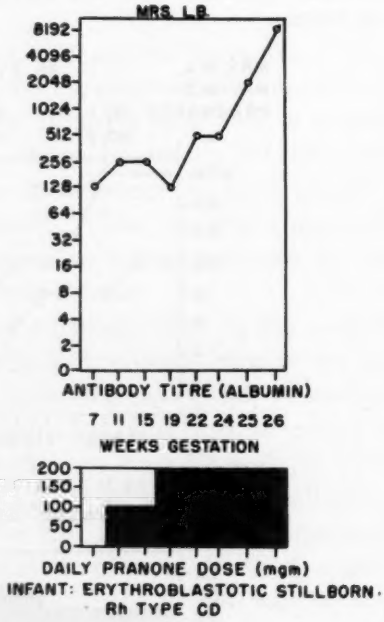

Fig. 3.

It will be seen that 8 of the 35 sensitized patients delivered Rh-negative infants. In 4 of these cases, the patients had previously delivered Rh-negative infants, indicating that the father was heterozygous, but, in the other 4, it had been assumed that the father was homozygous Rh positive. We have found that it is very dangerous, on the basis of Rh studies of the father, to decide that he is homozygous Rh positive. Until we have available HrD antiserum, there is no way to be certain about this point. The course of the antibody titer during pregnancy is also a poor indicator of whether or not the fetus is

Rh negative. Figs. 1 and 2 illustrate this point. In both of these instances, Rh-negative infants were delivered despite the fact that in one case the titer gradually fell during pregnancy, while, in the other, the titer rose.

The next two figures show the course of the antibody titer and ultimate outcome of two cases in which the mothers had previously lost erythroblastotic babies. Both of these patients received large doses of Pranone over long periods of time. Both delivered erythroblastotic infants (Figs. 3 and 4).

There is some evidence to indicate that cortisone or its progenitor ACTH might be effective in combating sensitivity states. The beneficial effect of these substances in hemolytic anemias in which circulating antibodies are present suggested that there might be a similar beneficial effect in cases of Rh sensitization. Therefore, we administered ACTH to 4 sensitized Rh-negative pregnant women in dosage of 100 mg. daily over a period of 7 to 10 days. All 4 of these patients ultimately delivered erythroblastotic stillborn infants. Al-

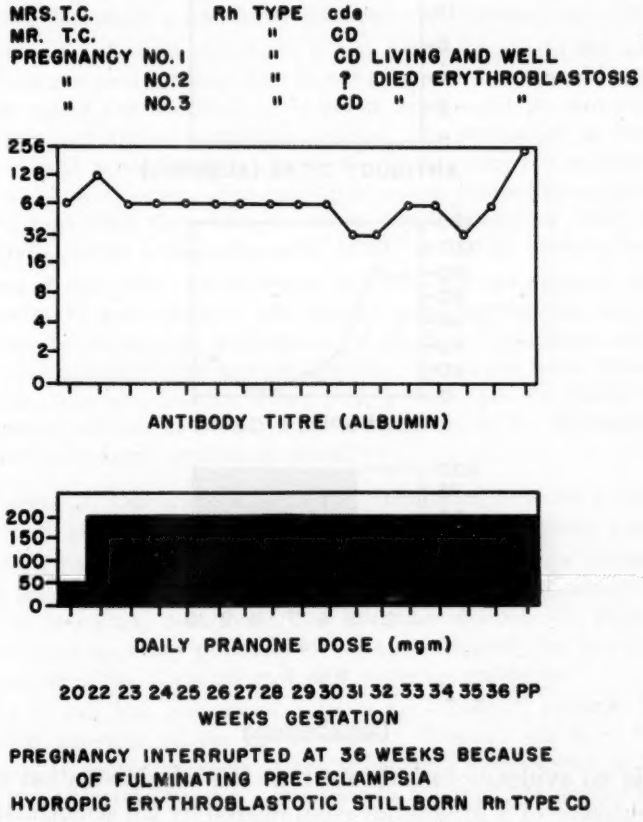

Fig. 4.

though in each case there was a drop in the circulating eosinophil count, indicating an ACTH effect, no change in the Rh antibody titer was evident. A typical response is shown in Fig. 5. Three nonpregnant sensitized patients were treated with similar results. One nonpregnant patient received cortisone. Although in this case there seemed to be a temporary drop in the titer level, antibodies failed to disappear from the blood.

Our pediatricians have been impressed with the apparent beneficial effect of ACTH on babies afflicted with hemolytic disease. Such infants seem to

maintain their hemoglobin at higher levels and show a more rapid disappearance of antibodies from the blood, following ACTH administration. In several instances in which the cord blood hemoglobin was only mildly decreased (about 14 Gm.), infants have done well on ACTH without transfusion. It is difficult to draw conclusions as to the effectiveness of therapy in such cases, however, for we all know that many of these would do well without any specific therapy. ACTH may be a valuable adjunct to the therapy in the newborn, but it should not substitute for transfusion, which is still the prime therapy in the newborn infant afflicted with hemolytic disease.

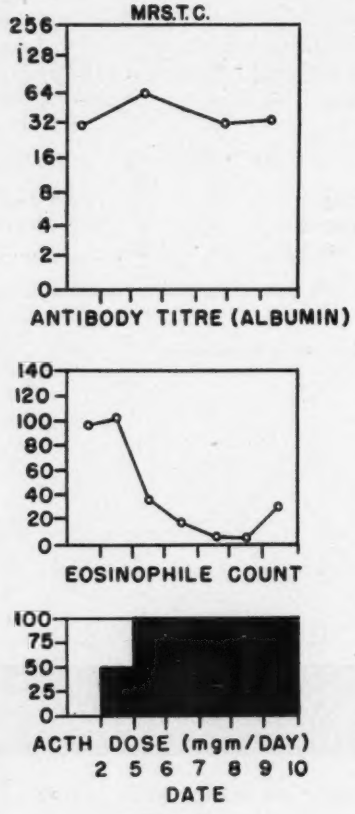

Fig. 5.

Conclusions

1. There is no evidence to indicate that the administration of Pranone will influence the outcome of a pregnancy complicated by Rh sensitization.

2. It would appear that ACTH is ineffective in desensitizing Rh-sensitized individuals, although its more prolonged administration should be carried out in order to answer this question more certainly.

3. ACTH appears to be a valuable adjunct to the therapy of the newborn infant involved by hemolytic disease.

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Discussion

DR. ALLAN C. BARNES, Columbus, Ohio.—In November of 1950 we started at Ohio State University a study similar to the one Dr. Holmstrom has so excellently summarized. In our instance, however, while all of the patients were sensitized Rh-negative women, none of them was pregnant at the time. We were primarily interested in the effect of various drugs on the antibody level independent of the presence of a fetus. Sixteen women volunteered for the study, and with their cooperation over a period of a good many months it was possible to test a wide variety of chemicals.

The drugs we were particularly interested in studying at that time were those which achieved adrenal cortex supplementation: cortisone, which is true cortical supplementation, and also its chemical neighbors—some of which were believed to have similar action—Pranone (anhydrohydroxyprogesterone), testosterone, ethinyl estradiol, d-5-pregneninoline, progesterone, and estrogenic substances. Control patients either received nothing or were given 5 grains of aspirin daily. Through the courtesy of Dr. Warren Wheeler, antibody levels were determined at weekly intervals and the patients received rather intense dosages. Dr. Irving Rothchild's laboratory followed the eosinophil and lymphocyte counts.

Since the severity of erythroblastosis is not proportionate to the absolute antibody level—severely damaged babies being born to mothers with low titers—we started with the fair premise that unless the antibody level could be brought to zero and would remain there, this approach held little therapeutic promise. To summarize as briefly as possible, we never achieved such a result with any of the medications tested, and no patient was permanently rid of her antibodies. The eosinophil counts showed no consistent trend under these drugs. We concluded that adrenal cortex supplementation itself would not solve this problem—adrenal cortex stimulation with ACTH not at the moment being our concern.

In the course of this study we confirmed the fact that the antibody levels determined at weekly intervals are not constant, but display some spontaneous rise and fall. This change in level can be reduced to a minimum, if the blood specimens are frozen and the entire group of determinations for any one patient run at the same time, rather than at weekly intervals as they are drawn. Using such a technique we found that while many of the drugs employed seemed to alter the antibody level, as Dr. Holmstrom has reported, none resulted in any permanent reversal of sensitivity.

DR. N. S. ASSALI, Cincinnati, Ohio.—Dr. Holmstrom is to be commended upon his daring experiment of giving ACTH and cortisone to normal pregnant patients.

I am not at all familiar with the sensitization, but I am more interested in the electrolyte and fluid balance of those patients who were particularly submitted to ACTH. I did not see any of this study mentioned, but I wonder whether Dr. Holmstrom has done any study of this kind on these patients, or whether clinically he has observed any rise in blood pressure or any clinical manifestation of water accumulation.

I would like to ask him also whether these pre-eclamptic patients he observed had received any ACTH previous to the pre-eclampsia. Recently we have been attempting, as I said yesterday, to reproduce some of the phenomena encountered in toxemia of pregnancy with ACTH and corticosterone. It seems to me that the dosage employed by Dr. Holmstrom is sufficient to produce electrolyte and fluid change.

DR. HOLMSTROM (Closing).—We administered Pranone to some nonpregnant patients as well as to pregnant women, and came to the conclusion (as did Dr. Barnes) that it had no effect, even in the nonpregnant patient. I do not know what dosage Dr. Barnes used, but we gave patients 50 mg. a day of anhydrohydroxyprogesterone and it had no influence on their menstrual cycles.

The statement regarding the variation in antibody titer from day to day is certainly something we have all seen.

Another point that I think bears stressing is that it is very dangerous to compare antibody titer levels between various laboratories. I have seen several patients who

were subjected to cesarean section on the basis of the fact that in one laboratory a titer was obtained at 1:16, and in another laboratory a couple of weeks later it was 1:56, and the physician got excited thinking something was radically wrong.

Concerning the questions regarding ACTH: We observed no effect in the patients who had normal pregnancies from the administration of the ACTH as far as change in blood pressure was concerned. The only thing we noted or paid attention to was the blood pressure and weight. We did not carry out electrolyte studies, so we have no information as to what effect the ACTH might have in pregnant patients in that regard.

The patients who developed pre-eclampsia were not patients who had received ACTH. In one patient with pre-eclampsia we were bold enough to give some ACTH for a few days to see whether we could influence it one way or the other, and we could not see that there had been any change as a result of the ACTH therapy.

IS SELECTIVE RIGHT LOWER QUADRANT SURGERY IN WOMEN CURATIVE?*

With a Report of 200 Cases Studied

W. O. JOHNSON, M.D., LOUISVILLE, KY.

THE patient constitutes the only reason for the existence of the physician. Let not the enthusiasm in our treatment of the patient blind us as to the truth of the end results.

This dissertation is not a presentation of a series of new drugs, new operative procedures, or a collection of excellent personal results, but is a retrospective study, which I think we all need to make at times.

The medical profession in the past has assumed the responsibility of the care and treatment of people who are sick, but, until recently, the profession did not distinguish between those conditions that arose alone from organic disease and the others that may arise from mental, emotional, or functional causes, nor do we now fully recognize the influence and the interchange of these, one with or over the other.

Emotional conditions may cause many impaired bodily functions and not be associated with laboratory abnormalities. They usually predominate with states of tension, nervousness, and associated conditions of fatigue, fears, etc. Functional disorders do not ordinarily conform to anatomical structural limits, and they are not usually constant. Nor are they always progressive, and in some cases may be present, and over a period of years be predominately centered, in one or a group of organs, in which, after repeated laboratory tests, nothing abnormal can be found, so that, after many careful pursuits, we are not able to find definitely the cause of the complaints. We should not shrug our shoulders and tell the patient that there is nothing wrong with her, "just nervousness," and for her to go home and forget it. In this era of specialization, let us be fair with the patient and pursue the study of the condition until the cause is found, and corrected if possible.

From the patient's viewpoint the symptoms of organic disease or functional disorders are the same. Both are just as disabling and disturbing to her, and the patient feels that they need study and correction, equally completely. We, as physicians, can no longer be content to say that a condition is "functional" and pass it off, because we cannot by our "laboratory procedures" find a cause to explain it. Nor should we be satisfied when the cause is found by a process of elimination, but the cause should be pursued, studied, and found by positive, direct evidence.

The patient is the first to become aware of signs and symptoms that differ from the normal, but she does not know how to interpret them properly; so

*Presented at the Nineteenth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Detroit, Michigan, Sept. 20, 21, and 22, 1951.

it is our responsibility, as physicians, trained in the interpretation of these changed signs and symptoms, to help the patient in the correct interpretation of her symptoms. With greater cooperation of patient and physician, and more diligent detection of early changes by both, we can detect many diseases earlier; thereby corrections are more easily made, and the permanency of good results is more definitely assured. It is the combined responsibility of the patient and the physician to know all they can about the disease and to correct it as early as possible, for the best results. The sooner the physician shares the responsibility of the illness with the patient, the quicker will he get the desired results. I believe that the doctor should permit the patient to become an active and informed participant in his own treatment rather than being only a passive recipient. Treat a patient as a child, and she will respond as such; treat an adult as an adult, and you will more often get an adult response.

This is not written to intimate that I anticipate entrance into the field of psychiatry or profess to be a psychiatrist, or expect to change the profession of surgery I have practiced for over thirty years, but to point out a changing attitude that I see in surgery of today, and to add my humble approval of it.

Material

I will present 200 cases in which there have been lower quadrant abdominal complaints and one or more surgical operations, without relief of the symptoms. In the study of these cases I hope to show a picture of physical and glandular inadequacies in patients who have been operated upon, with the results obtained, and to present a possible insight into the cause of their complaints.

These cases constituted 11 per cent of over 2,000 cases studied. The patients were operated upon by a number of different surgeons, and they have three things in common: (1) All of them had appendectomies, singly or combined. (2) The symptoms either existed before the operation and were not relieved and/or were made worse after the operation. (3) The patients were still seeking a cause or a cure of their complaints.

To present these findings as briefly as possible, I will endeavor to embody the group of 200 cases in the form of a case history, presenting the finding only when it occurred in over 30 per cent of the cases studied.

Mrs. P. M. S. is a fairly well-developed, undernourished woman of 25 years (age range from 17 to 48).

Chief Complaint.—

1. Pains in lower abdomen	45%
2. Weakness and nervousness	42%
3. Excessive periods	35%
4. Backache	34.5%
5. Nausea and vomiting	31%
6. *Other symptoms of importance:*	
1. Insomnia (Not refreshing sleep—55%)	49%
2. Nervousness	46%
3. Anxiety and fears	32%
4. Dyspareunia, frigidity, and high divorce rates are common	

Menses.—Began on an average of 12.6 years

1. Either over six days or under three days	40%
2. Perpetually irregular	38%
3. Vaginal discharge	32%
4. Depression and swelling of hands and feet before the period	30%
5. Dysmenorrhea	25%

Physical Findings.—

1. Small uteri (29.5 per cent posterior fixed)	54%
2. Physical exhaustion and pelvic congestion	51%
3. Cold and clammy extremities	40%
4. Blood pressure less than 100/60	34%
5. Secondary anemia—hemoglobin 77.9 per cent or less	30%
6. Flattening of vaginal mucous membrane	30%
7. Cystic ovarian enlargement	24%

Could the above groups of findings be attributed alone to an inflamed appendix?

A review of the fertility rate of this group is of interest. The majority were or had been married:

1. 65 had no pregnancies (32.5 per cent sterility)
2. 58 had one child
3. 22 had two children
4. 22 had three children
5. 7 had four children
6. 1 had five children

110 women had 201 children

There were recorded 24 miscarriages in the group. Some of these patients were greatly disturbed by their apparent sterility. In those cases where there was no improvement of symptoms after operation, the same symptoms were greatly aggravated by subsequent pregnancies. If the patient's adjustment to her environment before the operation or pregnancy was inadequate, could one expect it to be improved with the increased responsibility? Yet quite a few had been told that their problem would be solved if they became pregnant.

Let us review the operations that were performed:

1. Appendectomy alone	65 cases
2. Appendectomy, partial oophorectomy, uterine suspension, and/or salpingectomy	54 cases
3. Appendectomy and (80 per cent right side) oophorectomy	36 cases
4. Appendectomy and suspension	25 cases
5. Appendectomy and hysterectomy	20 cases
	200 cases
6. Removal of ovarian cyst, 87 per cent secondary operations	23 cases

In addition to the above there were suspensions, perineorrhaphy, gall bladder, and thyroid operations.

16 patients had 2 operations
14 patients had 3 operations
6 patients had 4 operations or more

In spite of repeated operations, the symptoms recurred after the operation and were not relieved by the operation. This did not deter the performance of future operations, but it did deepen the fixation in the individual and aid in the development of an escape mechanism. Of these cases 133 have been seen by me in the past four years. A year or more of time had elapsed since the operation. The average length of time from operation to examination was six years, and in five cases there was a duration of symptoms over a period of fifteen years. After careful study it was found that all these patients had had symptoms before the operation that were not relieved by the operation, and in over 35 per cent of the cases were made worse. In this group of cases we found what we thought the cause of the trouble to be as follows:

1. Situational reactions or neuroses	41 cases
2. Physical and glandular inadequacies or inadequate personalities	41 cases
3. Anxiety neurosis	40 cases
4. Adult maladjustment	39 cases
5. Family problems	31 cases
6. Depressions	8 cases
Total:	200 cases

From this group over 20 per cent were sent to psychiatrists, and it was with the help of psychiatrists that this classification was made. Over two-thirds of the above group can be helped by common-sense advice and teaching the patient how to live with herself. The help of psychiatrists is not needed.

Comment

An analysis of the histories shows that none of the patients had a textbook history of acute appendicitis. In the majority of these cases, they were operated upon as selective surgery, with an indefinite diagnosis of appendicitis, and at the time of operation an ovarian cyst was found.

With our wider concepts as to the cause of symptoms, should we not, either by positive elimination of the cause, or by more careful study of this type of case beyond the laboratory findings, or by consultation with psychiatrists, have a more conservative attitude about lower right quadrant surgery in women? We should give special care to the person whom we find by examination and study to be a physical and glandular inadequate, for in this group we find the most numerous complaints, with fewer organic changes and positive laboratory findings.

Removal of the organs because they have not adequately produced the desired functional results will not improve the individual, but will lower her reserve and render her less adequate to have the desired function later. Some of the organic inadequacies are the result and not the cause of their complaints, and if the cause is not relieved the results will not be satisfactory.

I believe that when repeated studies and laboratory examinations fail to reveal the cause, we should assume the attitude of watchful waiting in regard to surgery. Aside from acute appendicitis and ruptured ectopic pregnancy—one of each occurred in this series (determined by the pathology reports)—we should not make emergencies out of such a group of cases.

The ovaries removed in these cases, where reports were available, had in over 90 per cent of the cases either retention, follicular, or lutein cysts, and these could have been the result of disrupted physiology, rather than pathology. Such inadequate individuals are prone to the formation of cystic ovaries because of the circulatory changes resulting from the associated pelvic congestion and the retardation of follicle absorption. Improvement of the general condition and careful watching of such individuals will be followed by reduction in size of, and a return to better function of, the ovaries, or assuredly better than if they were removed. These people are not having "female trouble," but are having trouble being females.

The goal of therapy in these cases as in all cases is:

1. Symptomatic relief of the patient.
2. Demonstration of the cause of the complaints and understanding by the patient of the cause and sharing with the physician the responsibility of correcting it.
3. Improvement of the total functioning of the individual, physically, physiologically, and psychologically.
4. Prevention of recurrences and complications by guidance and specific instructions to the patient and cooperation with the patient.

We, as physicians, have the responsibility of teaching the patient the proper interpretation of her complaints and symptoms. If we are not interested in this phase of the case, we should send her to someone who is interested and is prepared to treat her.

If we do not have time to explain to the patient her symptom complex, we are only neglecting her and encouraging her neurosis, by operating upon her, or by pushing her off with "it is all caused by 'nervousness,' nothing is wrong with you, go home and forget it." This cannot be done; for the patient's complaints and symptoms are real to her, and she might have spent several years developing the symptom complex of which she complains. They cannot be discarded so early or so rapidly, nor can they be covered up or diverted by a series of shots, which are only temporary escape mechanisms. We should be diligent in finding the cause of the patient's complaints and never satisfied (when possible) with less. If we are not interested in doing so, we should send the patient to someone who is interested and who will find the cause of the complaints and be prepared to treat them.

In 20 per cent of these cases one can, if diligent enough, expect to have most appreciated results. The remainder continue to shop from one doctor to another, or for other forms of treatment or cults, seeking a "face-saving" method to continue their mode of life aided by needles, nostrums, and surgery until they become hopeless invalids or profound neurotics, because they do not have the intestinal fortitude to face the facts of life.

Is this not a challenge to the profession in the form of community health, education, personal cooperation, and guidance? Some surgeons state that "it can't be cured unless it can be cut out." We find in this group that even when it is cut out, they are not cured! Cure is impossible because they have the wrong treatment for the improper diagnosis.

With the use of chemotherapy and antibiotics, and the demands of the patient to administer "wonder drugs," the present tendency in the treatment of patients is impirical therapy, and this either avoids or delays the correct diagnosis in these cases. This attitude is also provocative of many mistakes. The finest cures are meaningless if based on the wrong diagnosis.

After all, doctors, drugs, surgery, and x-ray still act mainly as Nature's helpers. Almost every treatment entails a penalty as well as a reward, particularly if not properly used. You can develop cancer from an overdose of the x-ray which may cure some types of the disease, when properly given. Immunity from the antibiotics and resistance to sulfonamides in later life may be harmful and disappointing when they are needed in lifesaving measures.

What we need is a more careful, painstaking history by a "general specialist" who is interested in and understands human beings, combined with a more profound knowledge of the patient by the doctor and of the doctor by the patient. When this is obtained—physical, physiological, emotional, mental, and social understanding of the patient's complaints and the causes, which in turn will produce more and better permanent results with less expense—the progress of medical care of the people will reach even higher levels.

Conclusions

1. Selective surgery is curative when the surgery removes the cause of the patient's complaints.

2. The finest cures and best surgery are unsatisfactory and meaningless if carried out on the wrong diagnosis.

3. When in doubt about the diagnosis, let a plan of watchful waiting be carried out in surgery.

4. Complete psychiatric study when indicated, before surgery, will make for more satisfactory end results.

Discussion

DR. GERALD L. MILLER, Kansas City, Mo.—I wish to commend Dr. Johnson for his courage and thank him for bringing to us an analysis of a group of patients who in general, I believe, are among the most poorly treated and managed in medicine today.

It is unfortunate and distasteful that we must accept a large share of responsibility for a group of patients, a cross section of which the essayist presented today. First, a measure of incapacity and disability in these patients is difficult. Morbidity is not necessarily a measure nor is limitation of activity of value as it is in orthopedics and mortality is rarely a major problem. Rather, these patients must be evaluated on the basis of their ability to fill their place in society and this requires a great deal of time-consuming study as Dr. Johnson has pointed out.

A number of points of interest seem worthy of reconsideration. These patients are all in the reproductive age group. Pelvic pain is common and psychosomatic signs of inadequacy were prevalent, namely, anxiety, weakness, nervousness, and insomnia. Physical findings of hypometabolism and vasomotor instability were common and physical exhaustion with pelvic congestion (noninflammatory) was observed in over 50 per cent. Finally, 100 per cent of the patients were classified as having psychosomatic disturbance, either true psychosis or functional trends strong enough to be noted. Further, the surgery done was, to a large extent, and I will gladly delete any case with satisfactory pathological findings, that type of unjustifiable surgery which makes Blue Cross and other insurance rates unusually high and makes necessary unduly low remuneration to the doctor for those justifiable procedures we must do in everyday practice.

After the analysis of the patients of whom the essayist speaks, I am able to arrive at the conclusion that these patients represent from a diagnostic standpoint two groups: First, those individuals who present undiagnosed disturbances existing in the allied specialty fields of urology, proctology, and orthopedics. In these only a more careful study of the patient will result in proper management and the elimination of unnecessary pelvic surgery. The second and larger group is composed of those with cyclic reproductive system pain with so-called pelvic congestion or early painful endometriosis and the commonly occurring superimposed psychosomatic overlay.

With this latter group I believe we must be particularly concerned. Much remains to be learned about this disturbance. Meanwhile, our therapy must not be harmful. It is obvious, therefore, that management should be largely nonsurgical.

Taylor has made the most recent noteworthy contribution to this problem by his "Congestion-Fibrosis Syndrome." However, in our group we have been more impressed with focal edema as a satisfactory explanation for this distressing entity. The regular appearance of edema histologically in these involved structures, together with the noteworthy work of Gamble on extracellular fluid and the well-accepted premise that estrogen-sensitized tissues exhibit great flux in water retention, makes it seem likely that the acuity of edema and its faulty regression are the likely reason for the symptoms in this picture. The systemic nature of the manifestations of this syndrome and the ineffective results with various methods of therapy would strongly suggest a multiplicity of factors—local and general—as important in etiology and pathogenesis.

Treatment, until more is understood of the physiology of these patients, will remain empirical and should be based on a proper evaluation of the patient, together with dehydrating regimes, postural drainage, support, thyroid extract, proper attenion to nutrition, and elimination of focal pelvic infection. If these factors are properly managed, the stabilization of the endocrine system will generally be spontaneous.

Alvarez and others have repeatedly stressed that the responsibility of the constitutionally inadequate patient is the doctor's even though the salvage is minimal. Certainly these patients are not to be further maligned by the trauma of unnecessary surgery.

DR. JOHNSON (Closing).—I wish to take my few remaining minutes to add to the psychiatric side.

Criticism could be brought up that one is presenting patients, and often there is nothing brought out by which we can help ourselves, by constant careful study. Through the courtesy of Dr. Louis Foltz, one of the psychiatrists in Louisville, I have gathered together some questions that can be asked of patients, which will give us an idea about the conditions with which we might be dealing, and afford us some opportunity of benefiting thereby.

There are six questions which may be asked these individuals, which will give one a lead as to whether there is some underlying psychic disturbance; thus we can wend our way into finding the right diagnosis:

1. Has there been evidence of any personality disorder in the patient's past life?
2. Is there evidence of disturbance in the patient's environment?
3. Is there evidence of anxiety about the patient's relationship with his environment?
4. Is there evidence of fear shown by the patient's attitude toward life?
5. Is the patient maladjusted at the present time?
6. How frequently was the patient sick in the past life? And of what illness did the patient complain?

I think those questions will give a little guidance and help in the estimation of some of these patients, and may avoid some of the unnecessary surgery.

TRACHEOTOMY IN ECLAMPSIA*†

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ECHOLS,[1] in 1950, demonstrated the value of tracheotomy in severe head injuries and considered the procedure superior to any other method of maintaining efficient aeration of the lungs in unconscious patients. He believes that "it should be performed promptly and unhesitantly in every patient unconscious from a head injury if it seems likely that the coma will persist more than twenty-four hours and if nonsurgical methods of maintaining an adequate airway appear to be inefficient."

Sheehan[2] found naked-eye lesions, either in the form of cerebral hemorrhages, cerebral softening, or meningeal hemorrhages, in 24 out of 67 true eclamptic patients who had more than one convulsion and 14 of 31 pre-eclamptics who died of coma with no convulsions or only a single convulsion. Recovery from eclampsia is usually excellent from a neurological point of view.[3, 4] It is estimated that no more than 3 per cent of all patients with eclampsia develop cerebral hemorrhage.[3] If cerebral hemorrhage, meningeal hemorrhage, or cerebral softening is observed in approximately 3 per cent of autopsies following death from eclampsia, perhaps then measures directed toward these cerebral lesions will improve the salvage rate. Conceivably, any measure of benefit when cerebral hemorrhage results from external trauma might be of aid in any case of cerebral hemorrhage from other causes. Proceeding upon this premise, we decided to employ tracheotomy as adjunctive therapy in patients with eclampsia who showed marked respiratory difficulty and failed to respond to more simple measures, or who gave evidence of cerebral vascular accident.

Tracheotomy has been reported as of value in poliomyelitis,[5, 6] tetanus,[7] and a variety of medical conditions[8] where respiratory depression due to obstruction of the tracheobronchial tree by secretions requires prolonged endotracheal aspiration. Recently its value in preventing pulmonary complications in postoperative and severely debilitated patients has been presented.[9] For the past several years tracheotomy has been used in the postoperative care of patients with brain tumors[1, 10, 11, 12] or cerebral abscess.[13] Most recently it has been described as a lifesaving measure in the therapy of aspiration of vomitus during anesthesia in obstetrics.[14]

Material

From Jan. 1, 1946, to Aug. 1, 1951, there have been 67 cases of convulsive toxemia admitted to the Tulane Unit, Charity Hospital, New Orleans. From July 1, 1948, to Aug. 1, 1951, there were 19 cases of convulsive toxemia admitted to the Huey P. Long Charity Hospital at Pineville, La.‡ Thus we have been

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‡Since July 1, 1948, the Department of Obstetrics and Gynecology, Tulane University, has been responsible for the Obstetric and Gynecologic Services at the Huey P. Long Charity Hospital, Pineville, La., as a "farming out" project. Senior residents from the Tulane Unit, Charity Hospital, are rotated through the Huey P. Long Hospital and are in complete charge of the Division of Obstetrics and Gynecology, aided by weekly consultation visits by members of the Department of Obstetrics and Gynecology, Tulane University.

responsible for the care of 86 such cases during the period here surveyed. We wish to emphasize that cases included in this report are only those in which convulsions occurred. Severe pre-eclamptic patients with coma and all other signs and symptoms of eclampsia except convulsions are not included. None of the many cases making up the latter group had a fatal termination.

Management

There has been but little change in the management of convulsive toxemia on our service since Jan. 1, 1946, other than the recent use of tracheotomy (Nov. 25, 1950). Sedation was accomplished by using morphine sulfate, Sodium Amytal, Demerol, or phenobarbital, alone or in combination. Magnesium sulfate was used in many instances. The quantity of fluids administered varied. In no case was "dehydration therapy" utilized nor was any attempt made to force fluid intake parenterally. Fluids were administered in most instances in quantities of 1,000 to 1,500 c.c. of 5 per cent glucose, sufficient to compensate the insensible loss, plus an added quantity equal to the urinary output each 24 hours. This is comparable to the manner in which we manage cases of lower nephron nephrosis.

In addition to the above methods aimed at control of convulsions, lowering of blood pressure, and maintenance of fluid balance, assurance of an adequate airway was an important feature in management. Many factors enter into the problem of respiratory distress and oxygenation in the eclamptic patient. Marked depression of respiratory rate as a result of sedation can occur, edema of the lung and/or pooling of secretions in the hypopharynx or tracheobronchial tree are frequently observed. Laryngospasm occasionally complicates the problem. All of these factors interfere with proper gaseous exchange and frequently lead to hypoxia.

The pathological physiology of hypoxia due to tracheal obstruction results from the increased demands for oxygen by the body as a result of the violent respiratory efforts exerted to overcome the obstructed pathway, an increase in the intrathoracic venous pressure due to these efforts, and the transmission of this increase to the cerebral veins and sinuses. The carbon dioxide content of the blood may be increased. These combined physiologic disturbances result in hypoxia of the cerebral vascular epithelium which in turn results in increased permeability of this membrane. The tendency to edema is thus increased. This vicious cycle which results from partial tracheal obstruction further increases venous congestion, increases the cardiac load, and may eventuate in cardiac decompensation. Pre-existent or concomitant heart disease further increases the possibility of cardiac decompensation. Intracranial pressure increases and in time, as a result of the changes of CO_2 and O_2 tension, the increased intracranial pressure and the edema depress the medullary respiratory center. This further embarrasses the already deficient respiratory tract.

Eclamptic patients frequently exhibit marked respiratory distress and hypoxia. Oxypenia can be so marked that the patient exhibits cyanosis. Respiratory distress is relieved in many cases by the use of metal or rubber airways, repeated aspirations of the pharynx, larynx, and trachea, and the use of oxygen by mask or nasal catheter. Occasionally, these methods of providing an airway for oxygen have been ineffective in deeply comatose eclamptic patients and the exhaustion resulting from violent respiratory efforts has necessitated artificial respiration for varying periods of time. It is in these patients, unrelieved or unimproved by such methods, that we advocate tracheotomy. Tracheotomy allows instant and repeated aspirations as well as administration of oxygen. The pool of secretions in the hypopharynx is by-passed and the not uncommon complication of aspiration pneumonia is minimized. In a previous

report[15] we recorded 5 cases in which tracheotomy was utilized by us in the management of eclampsia. This report includes those 5 cases and 5 additional cases performed since then.

Tracheotomy has been used by us in 8 cases of convulsive toxemia, and in 2 cases of nonconvulsive toxemia. A brief abstract of each case follows.

CASE 1.—P. C., Charity Hospital, New Orleans. A 27-year-old Negro, gravida iii, para ii. In November, 1950, at about 36 weeks' gestation, she had a generalized convulsive seizure for approximately 3 minutes. Blood pressure was 220/140. Oliguria and albuminuria were present. She was sedated with morphine and phenobarbital. An intravenous fluid regimen was begun. Twelve hours later there was no improvement. Her breathing had become labored and was not improved by an airway with suction and nasal oxygen. A tracheotomy was performed and the patient's respiration became noticeably improved. She was delivered by cesarean section, under local infiltration and nitrous oxide and oxygen anesthesia. A premature infant was delivered. The patient's condition then improved steadily. The tracheotomy tube was removed on the fifth postpartal day and the patient was discharged on the tenth postpartal day. Check-up in the clinic six weeks later showed the patient to be entirely well.

CASE 2.—A 19-year-old Negro woman, gravida iii, para 0, was admitted to the Huey P. Long Charity Hospital at Pineville, La., with pre-eclamptic toxemia a few days before term. She responded well to toxemia regimen and delivered twins on Jan. 6, 1951, and had an uneventful hospital stay. She was discharged on the sixth postpartal day with a blood pressure of 112/70 and without any proteinuria or edema. She was readmitted 2 days later with a history of having had two convulsions. The blood pressure was 130/60, pulse 116, and the urine contained albumin. Despite heavy sedation another convulsion occurred. At midnight of the same date another convulsion occurred. The next morning, despite the fact that no more convulsions occurred and the blood pressure remained normal and proteinuria was no longer present, she had marked respiratory difficulty. Nasal oxygen and suction failed to improve the latter. A tracheotomy was performed and marked improvement was noted. The tracheotomy tube was removed five days later and the patient was discharged shortly thereafter in excellent condition. The final diagnosis is postpartal eclampsia or cerebrovascular accident secondary to pre-eclampsia.

CASE 3.—L. C., a 16-year-old Negro, gravida i, para 0, was admitted to Charity Hospital, New Orleans, La., in labor at about 35 weeks' gestation, with edema, proteinuria, hypertension, coma, generalized convulsions, and numerous coarse râles throughout both lung fields. Sedation and fluid therapy were given. Approximately one hour following admission the patient stopped breathing, the pulse was imperceptible, and there was no audible blood pressure. An emergency tracheotomy was performed. Immediately respirations were resumed, a pressure reading of 60/50 was obtained and a pulse rate of 120 per minute recorded. In three hours the blood pressure rose to 110/90. Delivery was accomplished per vaginam a few hours later. The tracheotomy tube was removed on the seventh postpartal day and the patient was discharged well on the eighteenth postpartal day.

CASE 4.—N. M., a 26-year-old Negro, gravida vi, para iv, approximately 32 weeks pregnant, was admitted to Charity Hospital, New Orleans, Feb. 28, 1951, having had many convulsive seizures prior to admission. She was in deep coma and had hypertension, edema, and albuminuria. Sedation, fluids, nasal oxygen, and tracheal suction were administered. There was continued marked respiratory distress and the respiratory rate fell to 10 per minute. A tracheotomy was performed and immediately breathing became easier. Spontaneous delivery of a premature infant occurred three hours after tracheotomy. The tracheotomy tube was removed five days later and the patient discharged well on the tenth postpartal day.

CASE 5.—C. M., 30-year-old Negro woman, gravida vii, para iv, approximately 30 weeks pregnant, had seven convulsions prior to admission and one after admission to Charity Hospital, New Orleans, on April 26, 1951. Hypertension, edema, proteinuria, and acute laryngospasm were present on admission. Tracheotomy was performed and there was immediate improvement of respirations. She delivered a premature viable female infant shortly thereafter. Postpartal improvement was steady and the tracheotomy tube was removed on the third postpartal day. She was discharged completely well on May 31, 1951.

CASE 6.—B. K., a 20-year-old Negro woman, gravida i, para 0, about 38 weeks pregnant, was admitted with coma, convulsions, laryngospasm, hypertension, albuminuria, edema, and coarse râles throughout both lung fields. No fetal heart tones were heard and definite evidence of a dead fetus and abruptio placentae was present. Sedation was given but did not improve the respiratory difficulty, so tracheotomy was performed 45 minutes after admission. Respiration immediately improved. The following day the patient's condition was generally improved but evidence of increasing severity in the signs and symptoms of premature separation of the placenta necessitated cesarean section under general anesthesia. A severe Couvelaire uterus was encountered which would not contract following removal of the baby, therefore cesarean hysterectomy was performed. One unit of fibrinogen was administered immediately for constant ooze from the wound edges. Following administration of fibrinogen, oozing of blood stopped. The tracheotomy tube was removed on the tenth postpartal day. On the twelfth postoperative day because of a serosanguineous drainage from the wound the patient was taken to the operating room and the wound examined under general anesthesia where it was found that the fascia had separated but the peritoneum was intact. Secondary closure of the wound was performed. From then on recovery was steady. The patient was ambulatory on the twenty-first postoperative day. A mild generalized convulsion followed by Jacksonian-type convulsions developed. During the entire postpartal course her blood pressure varied between 142/80 and 184/118. On the twenty-fifth postoperative day she had a generalized convulsion. Reconsultation with the Departments of Medicine and Neurosurgery led to the diagnosis of hypertensive encephalopathy. Lumbar puncture showed clear fluid at a pressure of 330 mm. water. There was no respiratory difficulty from the time the tracheotomy tube was removed until the series of convulsions on the twenty-fifth postpartal day at which time the patient died. Permission for autopsy was not granted.

CASE 7.—L. S., 21-year-old para 0, gravida i, was admitted to the Huey P. Long Charity Hospital at Pineville, La., on June 14, 1951. She was approximately 28 weeks pregnant and had hypertension, edema, proteinuria, coma, and convulsions. Râles were found in both lung fields. Sedation, nasal oxygen, intravenous fluids, and digitalis were administered. Twenty-four hours later, the patient was in poor condition, the blood pressure was 118/60, she remained in coma, and marked respiratory difficulties developed. A tracheotomy was performed with improvement in respiration but the patient died a few hours later. Autopsy showed marked edema of the brain but no evidence of softening or hemorrhage.

CASE 8.—D. D., 18-year-old Negro woman, was admitted to Charity Hospital July 16, 1951, with hypertension, edema, and albuminuria. She was placed on the toxemia regimen. She delivered spontaneously on July 18, 1951, and sedation was given immediately after delivery. One and one-half hours thereafter she had a generalized convulsion. A few hours later another generalized convulsion occurred with marked laryngospasm. Tracheotomy was performed with immediate improvement in respirations. Five days later the tracheotomy tube was removed and patient was discharged well on the twelfth postpartal day.

In addition to tracheotomy in the previous 8 cases of convulsive toxemia, there were 2 cases of nonconvulsive toxemia in which the procedure was utilized.

Though this paper and all statistics contained herein are based on our experience with convulsive toxemia, it is not amiss to include a brief description of these latter two cases in order to emphasize the value of tracheotomy in the field of toxemia.

CASE 9.—L. C., a 30-year-old Negro woman, gravida vi, para iii, was admitted Nov. 25, 1950, approximately 30 weeks pregnant, with a history of headache. There was marked hypertension, edema, and proteinuria. She was placed on the toxemia regimen. Approximately 14 hours after admission the blood pressure continued to rise, the urinary output was diminished, and marked respiratory difficulty developed which was unrelieved by tracheal intubation and aspiration. Therefore a tracheotomy was performed. The patient's respiratory difficulty was immediately relieved. Seventeen hours after admission, a premature stillborn infant was delivered. The tracheotomy tube was removed on the fifth postpartal day and the patient was discharged well on the twelfth postpartal day.

CASE 10.—D. B., 19-year-old Negro woman, gravida i, para 0, was admitted, approximately 36 weeks pregnant, on June 23, 1951, to Huey P. Long Hospital, Pineville, La., with marked hypertension, proteinuria, oliguria, and edema. Sedation and intravenous fluids were administered. Twelve hours later, nasal oxygen was started as respirations had become very labored and shallow. Shortly thereafter respirations decreased to 3 to 4 per minute. An emergency tracheotomy was performed with the patient still in her bed and immediately her respirations became near normal. Soon afterward a low cesarean section was performed using local anesthesia. On the sixth postpartal day, the tracheotomy tube was removed and the patient was discharged on the twentieth postpartal day.

Comment

Of the eighty-six patients with true convulsive toxemia managed by us from Jan. 1, 1946, to Aug. 1, 1951, seven died (8 per cent). We wish to reemphasize that, had we included in this series the many cases of severe toxemia exhibiting coma, proteinuria, edema, and hypertension, but not convulsions, the mortality rate would have been much lower, as none of these latter patients died. Of the seven who died, two had the benefit of tracheotomy. In one of these a second and fatal cerebrovascular accident occurred 13 days following removal of the tracheotomy tube and apparent recovery (Case 6). In the other case the tracheotomy was performed much too late (Case 7). We believe that many of the eight patients having tracheotomy would have died had the procedure not been used. Of the five who died prior to our utilization of tracheotomy, four died within 24 hours of admission, exhibiting marked respiratory distress. The other patient died 4 days after admission with respiratory failure a prominent symptom. We believe some of these might have been salvaged had tracheotomy been used. We do not advise that tracheotomy be used in every case of eclampsia. We advocate its use in patients suspected of having cerebrovascular accidents where respiratory distress is a prominent symptom. We believe it to be indicated in other cases of toxemia where there is interference with normal respiration by obstruction high in the respiratory tract unrelieved by simpler means.

Conclusions

1. Tracheotomy can mean the difference between survival and death in cases of eclampsia.

2. It is indicated in cases where airways and suction fail to maintain adequate ventilation of the lungs or where laryngospasm develops.

3. Tracheotomy sets should be a part of the equipment in all delivery units.

4. No ill effects from tracheotomy have been observed by us in any case in which we have used the procedure.

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Discussion

DR. STANLEY T. GARBER, Cincinnati, Ohio.—We are indebted to the authors for pointing out that tracheotomy in eclampsia, as well as in other conditions including prolonged unconsciousness, is an efficient method for maintaining aeration of the lungs. In two of their cases, namely, Case 3 and Case 5, tracheotomy done soon or immediately after admission was perhaps a lifesaving measure. In the former case, after complete cessation of breathing, immediate improvement occurred following tracheotomy. In the latter case, with acute laryngospasm on admission, tracheotomy was beneficial.

From this point on, I am impressed only by the ineffectiveness of the method of treatment of convulsive toxemia in which, to quote the authors, "There has been but little change . . . on our Service since Jan. 1, 1946, other than the recent use of tracheotomy." I might add that this applies throughout this country and abroad as well, where the number of eclamptic patients who die is far too great. Prevention is of course the ultimate goal, but does not fall within the scope of this discussion.

With the remaining eight cases presented, let me illustrate:

1. That ample time was present for effective treatment to become established, and
2. That by their own admission the treatment was ineffective.

In 6 cases the elapsed time between beginning of treatment and tracheotomy ranged from 12 hours up to 8 days plus 12 hours. In one case no time was mentioned except that sedatives had time enough to depress the respirations to 10. In one case there was only 45 minutes.

The problem of eclampsia has for years been approached from the wrong end, namely, the treatment of terminal symptoms and signs—multiple convulsions, prolonged unconsciousness, and pulmonary edema. By studies directed at the disturbed pathophysiological phenomena of these individuals, we have progressed in our knowledge of the underlying abnormal vasopressor activity from which result the varied symptoms and signs. The inciting mechanism is still undetermined. High-protein, low-sodium diet with liberal fluid intake may reverse the process in some cases.

Together with pathophysiological studies, the vasodepressor activity of various drugs has been observed and tested. Among these, the veratrum alkaloids used empirically but effectively for many years in Cincinnati remain unsurpassed to date in overcoming the abnormal arteriolar spasm in pre-eclampsia and eclampsia alone, or when superimposed on pre-existing chronic hypertension. When given intramuscularly or preferably intravenously in 5 per cent glucose in distilled water, veratrum almost immediately produces a marked arteriolar vasodilation with a consequent drop in blood pressure. It has been recently demonstrated that veratrum preparations do not act on the veins. Hence, postural hypotension is not present as with sympathetic blockading agents, such as tetraethylammonium chloride and spinal anesthesia. The drug also does not affect the cardiac output. Urinary output is not impaired. Thus the available evidence indicates that an integrated ar-

teriolar vasodilation with a decrease in peripheral resistance and increased blood flow to the major organs is the result of veratrum administration. Improvement of the circulation occurs and oxygenation improves. The vicious cycle of abnormal vasoconstriction, diminished blood flow, anoxia, thrombosis, edema, hemorrhage, and necrosis is broken. Convulsions cease without sedation—other than magnesium sulfate which is of benefit.

Fluids from 3,000 to 5,000 c.c. daily are given with excellent diuretic effect. This condition is not comparable to lower nephron nephrosis, either pathologically or clinically.

We feel that sedatives in large amounts, as employed almost universally elsewhere, obscure and prolong unnecessarily the unconscious state contributing definitely to respiratory embarrassment and pulmonary edema.

The authors report an uncorrected maternal mortality of 8 per cent (7 deaths in 86 cases of convulsive toxemia). In a series comparable in every respect to the series reported, we have an uncorrected maternal mortality of less than 1.5 per cent. (In over twenty years, three deaths have occurred in 204 consecutive convulsive eclamptic cases, two from sepsis early in the series, one from eclampsia per se.) We have found tracheotomy unnecessary.

Tracheotomy has a place whenever upper tracheal obstruction is unrelieved. When eclampsia is promptly controlled, as it can be, tracheotomy becomes unnecessary.

DR. COLLINS (Closing).—We did not imply nor did we write that the pathology in eclampsia is the same as in lower nephron nephrosis. We merely stated that our fluid balance regimen is the same as advocated for lower nephron nephrosis. We do not think we can increase kidney function and promote diuresis by pushing a lot of fluid into an already damaged kidney where there is an arteriolar spasm.

As regards the time lapse between the onset of therapy and the onset of tracheotomy, we could very well tracheotomize every eclamptic who comes in, but I think it is better proof of the value of the procedure if we allow the patient to go on with our usual regimen. If she shows no improvement we then do a tracheotomy.

The mortality rate of 1.5 at Cincinnati is excellent. We are not too proud of ours, and we are trying to improve it. In Memphis, Dr. Frank Whitacre told me he had five deaths in 100 or more cases, and he said all of those patients died of cerebral hemorrhage. If both Dr. Whitacre and Dr. Garber would add tracheotomy to the management of the patients who are not dying, perhaps their excellent results would be superior. We hope that the Cincinnati group do not take as long to employ tracheotomy as we in New Orleans have been in using veratrum viride.

EFFECT ON CESAREAN SECTION BABIES OF STRIPPING OR MILKING OF THE UMBILICAL CORDS*†

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(From Harper Hospital and Highland Park General Hospital)

IN CESAREAN section there is an inescapable tendency to clamp and cut the umbilical cord as soon as the child is extracted so that he can be removed from the operating table. This permits the operator to direct his immediate attention toward the prompt control of maternal blood loss and closure of the uterine wound. Theoretically, this early interruption of the fetal-placental circulation would tend to deprive the child of blood, which, with more delayed clamping of the cord, could possibly flow from the placenta into his body. Even if this is the case, it is probable that the loss would be of only minor importance to well-developed and normal babies. However, under other circumstances, prematurity, for example, failure in this way to obtain an appreciable amount of extra blood could have serious consequences. It might even be the cause of some of the otherwise unexplainable fetal deaths associated with cesarean section. Consequently, we investigated the blood of cesarean section babies to determine: (1) hemoglobin and red blood cell levels with the usual, immediate clamping and cutting of the umbilical cord, and (2) the effect of rapid stripping or milking of the cord toward the baby before it was severed.

In the literature we were unable to find any substantial studies giving blood counts on babies delivered by cesarean section. A few authors have expressed the belief that they might be lower than in vaginally delivered babies. Landau, Goodrich, Francka, and Burns[1] went so far as to ascribe a considerable part of the mortality in cesarean section babies to anemia. These writers, though noting the peculiar difficulties of respiratory onset in certain cesarean babies which were attributed by Bloxsom[2] to a failure to condition the infant by uterine contractions or passage through the birth canal, were more impressed by another group. These babies, they pointed out, developed symptoms 2 to 4 hours post partum consisting of cyanosis, respiratory distress, air hunger, costal retraction, and rapid, weak pulse. They then failed rapidly and died 18 to 20 hours later without being appreciably benefited by oxygen, incubators, caffeine, etc. Landau and his co-authors cited Potter's[3] opinion that such death was due to intracranial pressure related to the type of delivery. Others have blamed it on aspiration pneumonia. The authors, however, thought the symptomatology suggested hematogenic shock. This, they

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speculated, could be brought about by the usual procedure of immediate clamping of the cord, which they thought would deprive the baby of a substantial amount of blood. On the basis of this idea, and apparently without advantage of blood counts or blood volume data, they carried out the troublesome scheme of leaving the umbilical cord intact and then elevating the placenta, after it became detached from the uterus, so that the placental blood might flow by gravity into the infant. In 87 cases so treated there was no instance of the shock syndrome, and the babies appeared so much better that no control series was felt to be justified. It is to be noted, however, that, regardless of any possible advantage to the baby in this plan of treatment, it fails to eliminate the fundamental objection to late ligation in that the presence of the baby on the operating table until separation of the placenta interferes with the prompt control of maternal bleeding and suturing of the uterine incision.

It is generally accepted that, in vaginal delivery, delay in severing the umbilical cord, at least until the pulsations have ceased, will substantially increase transfer of blood from the placenta to the child.

Haselhorst and Allmeling[4] in their several studies found that newborn babies placed immediately on scales would eventually gain an average of nearly 100 grams. On the other hand, the less known but similar and even earlier investigation in this country by Williamson and Taylor[5] showed a final average gain of a mere 4 or 5 grams. This slight gain was believed to be due to the filling of the child's pulmonary circulation as it opened up with the establishment of respiration. Pointing out that the fetal-placental circulation is a closed one, they stated, therefore, that any blood which enters through the umbilical vein does so only because a like amount is forced out of the baby and into the placenta through the umbilical arteries by cardiac action of the fetus. They furthermore found that their babies with immediate ligation gained weight just as well as those with late ligation of the umbilical cord. All in all, though, studies of this kind and those from the standpoint of blood volume, weight gain, and general welfare[6, 7, 8] seem to have established that vaginally born babies derive a substantial degree of benefit from late separation from their placentas. Actually, though, the advantage to the cesarean section baby could be much less because of the loss of intrauterine pressure and pumping action on the placenta due to the incision through the uterine muscle wall.

Granting, then, that there are probably advantages to the vaginally delivered baby in late ligation of the umbilical cord, it is also true that in cesarean section such advantages (even if possible) could be obtained only at the expense of interference with and dangerous delay in attention to control of maternal bleeding and closure of the uterus. Consequently, we decided to try the effect of immediate and rapid stripping or milking of the umbilical cord from the still-attached placenta toward the baby. Aware of the old warning in some textbooks that this procedure might dangerously overload the circulation, it was first tried out in well over 200 vaginally delivered babies. There was no evidence of any injurious result whatsoever. McCausland, Holmes, and Schumann[9] tried this same technique in 50 instances, and they also saw no ill effects.

Material and Methods

Observations were made on 100 babies delivered by cesarean section at Harper Hospital and Highland Park General Hospital. The cases were unselected except for the elimination of stillborn babies, or cases where there was the possibility of hemorrhage from the fetal-placental circulation due to the extension of the uterine incision into the placenta.[10] In one hospital the umbilical cords to the boys were promptly clamped and severed in the usual way, while with the girls the cords were rapidly but thoroughly milked or expressed toward the babies before cutting. In the other hospital the sexes were reversed for the procedure. In order to allow for blood volume adjustment (which was reported by Ballentine[8] to be very rapid in the newborn), blood counts, hemoglobin determinations, and smear examinations were done after the second hour (but before the twelfth hour) of the first day, and then they were repeated approximately 48 hours later as a check. There was no evidence of Rh incompatibility in any case. The early blood counts and hemoglobin levels showed surprisingly little deviation from those taken after 48 hours. The first-day average determinations in the series of 100 babies were 16.5 grams of hemoglobin per 100 c.c. of blood and 5,061,000 red blood cells per c.mm., as compared to figures of 16.0 and 5,053,000 later. As this close correspondence also held good for all divisions of the series, it seemed sufficiently accurate to use only the first-day results in subsequent comparisons.

Results

Before taking up the principal object of the investigation, mention can be made of certain incidental observations of interest. First of all, it should be stated that with the cesarean section babies, as with those delivered vaginally, there was no apparent ill effect from forcing in blood by milking or stripping the umbilical cord. Since the point seems to have been hitherto ignored, it is worthy of note that there was very little sex difference in our babies. For the boys, the first-day hemoglobin average was 16.8 Gm. (110 per cent) and the red blood cell count 5,060,000, while for the girls the averages were 16.3 Gm. (105 per cent) and 5,062,000. It can be stated here also that, in spite of some ideas to the contrary, the fetal blood counts showed no recognizable relationship to hemorrhage and anemia in the mothers. Among the 8 instances of placenta previa and 2 of premature separation of the normally implanted placenta the lowest infant red blood count was 4,330,000 with a hemoglobin reading of 14.0 Gm. (91 per cent), and the averages were 5,400,000 and 17.3 Gm. In the 3 babies delivered of mothers who were anemic for other reasons and had hemoglobin determinations below 9.0 Gm. (59 per cent) the lowest infant hemoglobin was 15.5 Gm. or 101 per cent. Prematurity likewise appeared to have no appreciable effect on the early blood picture. In the whole series of 100 there were 10 premature babies who weighed less than 5 pounds, 8 ounces (2,500 grams). One of these had a low hemoglobin level of 12.8 Gm. (83 per cent) and red cell count of 3.91 million, but the averages for the whole group of 10 were 17.0 Gm. hemoglobin (111 per cent) and 5.01 million red blood cells. Furthermore, the smallest of the premature babies (all under 5 pounds or 2,270 grams) had no more tendency to initial anemia than the other 5 who weighed at least 5 but less than 5½ pounds.

The 50 babies in the series whose umbilical cords were cut immediately in the usual way had an average hemoglobin reading of 15.9 Gm. (103 per cent) and a red blood cell count of 4.76 million; whereas, for the 50 with rapid milking or stripping of the cords before clamping, the readings were 17.2 Gm. of hemoglobin (112 per cent) and 5.35 million red blood cells. This represents an average increase of approximately 8.5 per cent in the hemoglobin levels

and 12.5 per cent in the red blood cell determinations for the group with stripping of the umbilical cords. Tables I and II illustrate the general tendency to higher blood counts obtainable in cesarean section babies with stripping or milking of the umbilical cords. Especially to be noted, we believe, is the fact that in the group in which this procedure was not carried out, there were some babies with a relative degree of anemia which could very well have an important bearing on the outcome in the presence of Rh incompatibility, prematurity, feeding difficulties, infections, etc.

TABLE I

HEMOGLOBIN (GM. PER 100 C.C. BLOOD)	12-12.9	13-13.9	14-14.9	15-15.9	16-16.9	17-17.9	18-18.9	19-19.9	20-20.9
Umbilical cords milked	0	0	7	8	9	10	10	5	1
Umbilical cords not milked	3	5	13	5	11	3	3	7	0

TABLE II

RED BLOOD CELLS (MILLIONS PER C.MM.)	3.50-3.99	4.00-4.49	4.50-4.99	5.00-5.49	5.50-5.99	6.00-6.49	6.50-6.99
Umbilical cords milked	0	4	8	17	15	3	3
Umbilical cords not milked	2	9	16	9	12	1	1

The progress of the two groups of babies while in the hospital was examined to determine whether or not there was a noticeable effect from stripping or milking the umbilical cords on the general welfare of those babies so treated. As there was only one death among the 100 babies (apparently from immaturity in a 4 pound, 8 ounce baby whose cord had been milked, hemoglobin 19.9 Gm.), no comparison of mortality is possible. Nor was there a sufficient number of small premature babies to permit a valid comparison of results in prematurity. However, if the baby who died, the 4 others weighing less than 5 pounds (2,270 grams) and who for this reason required a prolonged hospital stay, and a sixth of full-term size but affected with diarrhea are deducted, there remains in the series of two groups a total of 94 babies who weighed 5 pounds (2,270 grams) or more at birth, whose course in the hospital was uncomplicated, and whose condition, therefore, offers a basis for contrast between the two groups. These babies were treated in essentially the same way; that is, both groups had about the same average stay in the hospital, and practically all babies were started on formula feedings within 24 hours after birth. As is our usual experience in cesarean section, the majority were discharged partly or entirely on formula feeding, only a few of the mothers having adequate lactation for full breast feeding. The two groups consisted first of 46 babies whose umbilical cords had been rapidly milked or stripped before clamping and 48 others whose cords had been clamped and cut immediately in the usual way. Table III seems to indicate some advantage for the first group.

TABLE III

	NO. BABIES	AVERAGE HOSPITAL DAYS	AT DISCHARGE			AVERAGE LOSS AT DISCHARGE
			UNDER BIRTH-WEIGHT	AT BIRTH-WEIGHT	OVER BIRTH-WEIGHT	
Umbilical cords milked	46	7.8	33 (71.7%)	1	12 (26.1%)	2.3 oz. (65 grams)
Umbilical cords not milked	48	7.9	38 (79.1%)	2	8 (16.7%)	3.8 oz. (107 grams)

Summary

Of 100 cesarean section babies, one-half had the customary immediate clamping and cutting of the umbilical cords. With the other 50 the cords were rapidly but thoroughly milked or stripped toward the babies before ligation. There was no ill effect from this procedure. In the first group the average hemoglobin reading was 15.9 Gm. per 100 c.c. of blood (103 per cent), and red blood cell count average was 4,760,000 per c.mm. For the 50 babies whose umbilical cords were milked or stripped the figures were 17.2 Gm. (112 per cent) and 5,350,000. Moreover, in the first group a few of the babies had a relative anemia which could have been of serious consequence in the presence of prematurity or complications of the newborn. On the other hand, among those whose cords had been stripped the lowest hemoglobin was 14 Gm. or 91 per cent. The progress of the babies from the standpoint of weight gain and loss indicated benefit from milking or stripping the umbilical cord.

There were several incidental observations of some interest. The fetal blood counts showed no relationship to hemorrhage or anemia in the mothers. There was very little sex difference in the blood counts. And finally, prematurity had no effect on the blood picture.

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Discussion

DR. HUBERT L. ALLEN, Alton, Ill.—This paper is of value because it calls the attention of obstetricians to a special phase of a problem which they have largely ignored, or dismissed as being of little consequence. Many of you received questionnaires from Dr. A. M. McCausland, a year or so ago, concerning the matter of stripping the cord, waiting for pulsations to cease, or clamping the cord immediately after delivery of the baby. Of the 1,198 diplomates of the American Board who responded to the inquiry, approximately two-thirds seemed to feel that the matter was of minor importance, while more than 800 did not reply at all.

Doubtless one of the reasons for our apathy is the fact that many obstetricians turn the newborn infant over to the pediatricians, and unless the latter express themselves strongly about the management of the cord blood as it relates to the baby's welfare, we are inclined to assume that it is of little significance.

The present study deals with the special problem of the cesarean baby, and is based upon the assumption that abdominal delivery alters the mechanism of the second and third stages of labor in such a manner that the baby does not receive the same increment of blood from placenta and cord as it does during the more gradual delivery per vaginam. In this connection it should be pointed out that it is rarely necessary for abdominal deliveries to be accomplished in a matter of seconds. With local, caudal, or fractional spinal anesthesia, and

using the lower segment approach, most cesareans can be as smooth, unhurried, and no bloodier than the average vaginal delivery. When the head is brought through the incision, there is plenty of time to let the contracting uterus aid in expulsion of the baby, thereby mimicking the normal second stage mechanism. While it is natural for the operator to want to dispose of the baby so that he can more quickly turn his attention to closure of the uterus, it is rarely necessary to sever the cord immediately, since maternal bleeding can be fairly well controlled by the assistant.

Regardless of the rapidity of abdominal delivery, the authors' figures strongly suggest the value of employing cord stripping as a routine in all cesarean section babies, nor is there any reason to doubt that it is also helpful to babies delivered vaginally. Five or six of the obstetricians who answered McCausland's query felt that there was some danger of increased icterus or intracranial bleeding, but these complications were not noted by the present authors nor by McCausland and his associates. In fact, everyone who has bothered to study this question of the effect of additional placental and cord blood being made available to the newborn infant feels that it is of definite benefit. Such was the conclusion of Landau and his co-workers who, while not stripping the cord, went to considerable trouble to deliver the placenta still connected to the infant by an intact cord, suspending it until the cord vessels had collapsed, usually in from six to ten minutes.

The present study is unique in that an attempt has been made to show the benefit of the additional cord blood by correlating blood counts, hemoglobin levels, and neonatal weight fluctuations. While the series is too small to be statistically conclusive, the results are encouraging, and it is to be hoped that the authors will extend their study over a greater period of time.

Stripping the cord is such a simple thing to do, requiring so very few seconds, that studies like this should recommend the procedure to all of us. Personally, I am a chronic "cord-stripper" and do it in all deliveries—whether vaginal or abdominal—except in cases where erythroblastosis is feared. I have not had a very scientific reason for following this routine; my reason for stripping cords has been that our pediatricians are much in favor of it, and feel that these babies do significantly better than others.

Original Communications

CONGENITAL AND ACQUIRED LESIONS OF THE UMBILICAL CORD AND SPONTANEOUS ABORTION*

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CONGENITAL and acquired lesions of the umbilical cord are seldom mentioned as possible etiological factors in spontaneous abortion. While the literature contains many articles on cord defects causing intrauterine asphyxia and the death of viable infants at, or near, term[3, 4, 5] only a few[3, 6, 7] mention cord abnormalities as the cause of death of previable embryos and fetuses. Two monographs on the pathology of the conceptus[1, 2] seldom mention cord complications. As has been stated elsewhere,[8, 9] it has been our policy, since June, 1947, to define any pregnancy terminating before 22 weeks' gestation, with a previable fetus weighing 500 grams or less, as an *abortion.* Preliminary study of 500 such cases, having tissue examinations in the pathological laboratory,[9] yielded 133 umbilical cords sufficiently complete for analysis, of which 31, or 23 per cent, were abnormal as follows: torsion 17, stricture 7, and true knot 7. Therefore, it seemed expedient to increase the number to a total of 1,000 cases and to report separately on cord complications as a factor in spontaneous abortion.

Materials and Methods

A total of 1,000 consecutive cases of spontaneous abortion were selected on the basis of tissue examination. They had been admitted to the obstetrical service over a four-year period, beginning June 1, 1947, and ending June 1, 1951. The total number yielded 297 cord specimens sufficiently complete for either gross or microscopic description, as shown in Table I, and these cases provide the basis for this report. Incomplete cords were not included even though the fetus appeared to be normal. Macerated and degenerated cords, per se, numbered 9 in all, and they were also excluded since these changes only reflected the state of the fetus. Consequently, 104 complete cords representing 10 per cent of the 1,000 cases, or 35 per cent of the total number of cords, were recorded as abnormal in Table II.

The abnormal conditions mentioned in Table II were culled from various articles on the umbilical cord, published during the past 50 years. Several of them, namely, achordia, or the absent cord, prolapse, vascular anomalies, edema, and the long and short cords are seldom mentioned. Achordia is offered as a term best describing absence of the cord, while coarctation is a descriptive term used to designate atresia and stricture of the cord and its vessels. Table II does not list such complications as: entanglement, varicosities, hematomas, cysts, tumors, thrombosis, spontaneous amputation, and the split cord since none of these were observed in our cases.

*This study has been supported by a grant from the Florida Citrus Commission.

Control data were obtained from a large group of 384 pregnancies, representing therapeutic abortion specimens (319) and unintentional abortions (65) under investigation for another purpose. The unintentional abortions occurred chiefly during gynecological operations for myomas of the uterus or uterine prolapse preceded by a curettage. There were 83 intact cords in this control group, four of which were abnormal, or 4.8 per cent, as shown in Table I.

TABLE I. INCIDENCE OF NORMAL AND ABNORMAL UMBILICAL CORDS IN SPONTANEOUS ABORTION AND IN THERAPEUTIC AND INCIDENTAL ABORTION SPECIMENS

	SPONTANEOUS ABORTION		(CONTROL) THERAPEUTIC AND INCIDENTAL ABORTION	
	NUMBER	PER CENT	NUMBER	PER CENT
Total number of cases	1,000		384	
Total number incomplete or unknown	703		301	
Total number of complete cords	297		83	
Number of normal cords	193	65.0	79	95.2
Number of abnormal cords	104	35.0	4	4.8
Total	297	100.0	83	100.0

Clinical Observations on Patients With Abnormal Cord Conditions

From the gross examination of many of the cord abnormalities, it was often possible to conclude that the fetal circulation had become obstructed, leading to intrauterine death of the previable fetus. This mishap can be suspected clinically, by a chain of events which may permit a presumptive prenatal diagnosis when the mothers have perceived fetal movement. They may observe a great flurry of fetal activity, followed by a loss of further movement. Thereafter, the uterus fails to increase in size, and the fetal heart is not heard, even though the pregnancy continues for several weeks. Breast engorgement may develop slightly, only to disappear. The clinical diagnosis is usually a "missed abortion." In time, cramps and vaginal bleeding may develop, after which a macerated or mummified fetus is expelled, weighing less than what one would expect from the menstrual age. Grossly, the placenta is fibrotic and the cord may have an abnormal condition. Microscopically, one sees hyalinized villi, which tend to be avascular, and there is usually much intervillous fibrin, and little, if any, decidual hemorrhage.

Results

As stated above, there were a total of 297 complete cords and of these, 104, or 35 per cent, were abnormal, as shown in Table I. The abnormal conditions listed in Table II may be grouped into congenital and acquired conditions as follows:

Congenital: Achordia without fetus, very short, very long, coarctation and vascular anomalies.

Acquired: Achordia with fetus, excessive torsion, knotting, prolapse, looping, and edema.

However, such division is not too practical since a congenitally long cord may undergo looping or prolapse, and thereby have an acquired complication. Such multiple lesions occurred in 14 cords, an incidence of 13.4 per cent. The various lesions will be discussed individually at this time.

Achordia.—Structural absence of the cord was observed in 52 intact specimens, or 50 per cent. These cases of achordia may be divided into two types:

1. Achordia without fetus, or complete absence of both embryo and cord: 43 cases, or 41.3 per cent.

2. Achordia with a stunted or nodular embryo lying free in the sac, without gross evidence of a cord: 9 cases, or 8.6 per cent.

TABLE II. LESIONS OF THE UMBILICAL CORD IN SPONTANEOUS ABORTION SPECIMENS

ABNORMAL CONDITION*	NUMBER	SPONTANEOUS ABORTION	
		NUMBER	PER CENT
1. Achordia without fetus	43	52	50.0
Achordia with fetus	9		
2. Very short cord	3	3	2.8
3. Very long cord alone	5		
Long cord and looping	3	11	10.5
Long cord and prolapse	1		
Long cord and torsion	2		
4. Excessive torsion	14		
Torsion and knot	1	16	15.3
Torsion and looping	1		
5. Looping alone	4		
Looping and coarctation	1	6	5.7
Looping and knot	1		
6. Coarctation alone	6		
Coarctation and looping	3	9	8.6
7. Prolapse alone	2	2	1.9
8. Twin pregnancy			
Absent cord one twin	1		
Looping and knot	1	2	1.8
9. True knot alone	1	1	0.9
10. Edema	1	1	0.9
11. Vascular anomalies, one artery absent	1	1	0.9
Total	104	104	100.0

*14 cords had two abnormal conditions or 13.4 per cent.

The first type is shown in Fig. 1, representing a placenta without evidence of either cord or fetus in the empty sac. Under such circumstances the amniotic fluid often contains a grumous sediment. Others[1, 2] have recorded similar observations. Congenital absence of both cord and embryo suggests improper development of the germinal disc from which they are derived.

The other type of "achordia with fetus" is seen in Fig. 2. Such specimens are presumptive evidence of a pre-existing cord lesion which may have caused death of the fetus, leading to subsequent expulsion.

Very Short Cord.—The average length of the cord is a relative matter corresponding approximately to the length of the fetus. For example, while a 1 cm. cord may be considered normal for a small embryo, it would be very short for a fetus with a crown-rump length of 10 cm. At term, the average cord length of approximately 55 cm. corresponds to the standing length of the child. A similar relationship can be made for early pregnancy, when the crown-rump length of the fetus equals the cord length, as shown by two specimens in Figs. 3 and 4. Experience with many such cases led us to designate a cord as short, when it was less than one-third of the fetal crown-rump length. By this standard, there were 3 short cords, or 2.8 per cent.

A short cord is not necessarily incompatible with intrauterine life and Browne[3] mentions two cases reaching viability. On the other hand, short cords were found by Mall and Meyer[1] when the fetus was either nodular or cylindrical. As with "achordia," mentioned above, whether or not the primary defect is in the cord or in the embryonic disc, or both, remains undetermined.

Very Long Cords.—Excessively long cords have been described in term pregnancies up to 181 cm. in length,[14] but scant mention is made in the literature of this condition in early pregnancy. From experience with cord lengths

in abortion specimens, it was arbitrarily decided that cords exceeding three times the crown-rump length of the fetus, were abnormally long, as in Fig. 5. This is in marked contrast to the normal, average length, stated above, which makes it equal to the crown-rump length. Using this criterion, 11 cords were considered as being very long, or 10.5 per cent. Very long cords were more likely to become involved in prolapse, looping, torsion, and knots as shown in Table II and Figs. 5 and 9.

Torsion.—Physiological torsion of the cord appears to be a normal phenomenon due to a spiraling of the vessels, as in Fig. 4. Spinning of the fetus may produce additional twists, involving the entire cord, as in Fig. 5, or be limited to certain segments, as in Fig. 6. Another common location is at the

Fig. 1.—Spontaneous abortion specimen composed of placenta and an intact, *empty sac* without evidence of either cord or fetus. This condition has been called "achordia without fetus."

Fig. 2.—Stunted nodular embryo (at arrow), lying free in the fetal sac without evidence of a cord, in effect, "achordia, with fetus."

fetal end, at the junction of the amnion with the squamous epithelium, as in Figs. 7 and 10. Here Wharton's jelly was deficient and only a half-twist was required to stop the circulation, in Fig. 7. A similar case was observed by Dale.[10]

Pathological torsion was observed in 16 cords, or 15.3 per cent, as stated in Table II. It may accompany looping, a long cord, or coarctation. Dorn[6] studied 64 fetal deaths due to torsion, and 33 of these were of fetuses under 5 months' gestation.

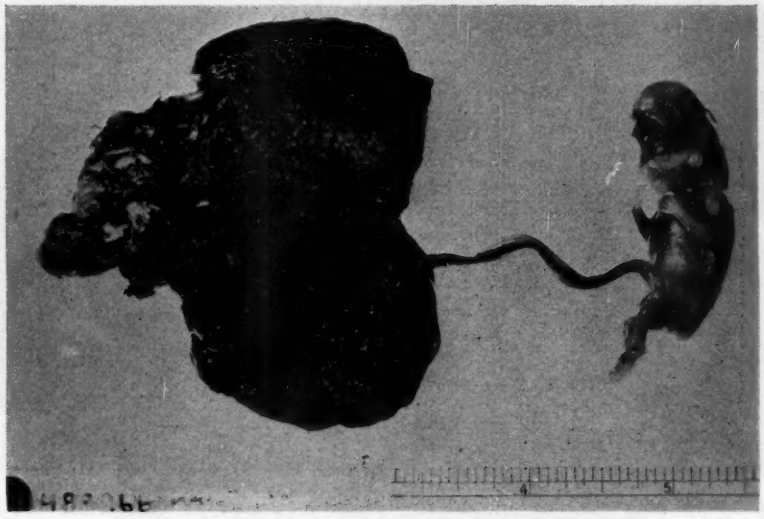

Fig. 3.—Macerated fetus of 3½ months' gestation, at which time average cord length is about equal to crown-rump length of fetus, as in Fig. 2. Cord was normal except for maceration.

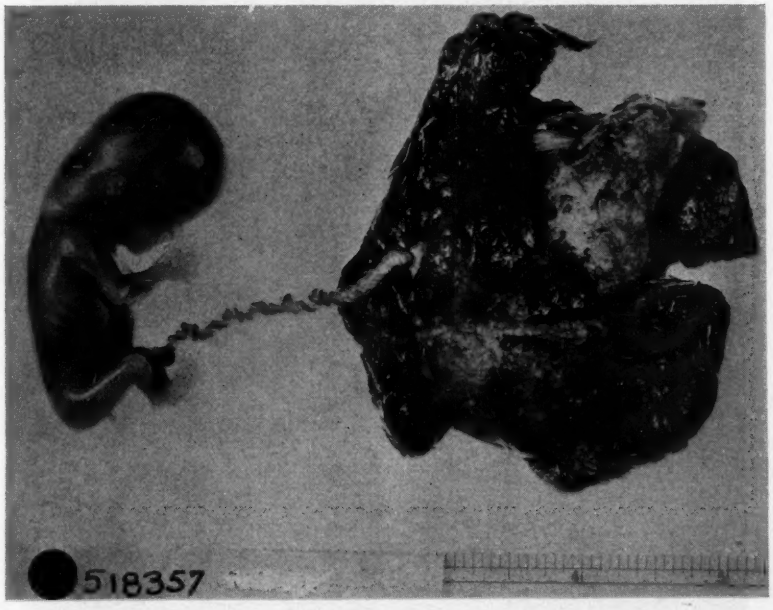

Fig. 4.—Normal fetus of 3½ months' gestation. Again cord length approximates crown-rump length of fetus, as in Fig. 1. Cord had exaggerated torsion, without effect on vessels, so it is regarded as normal.

Looping of Cord.—Simple looping is probably a common physiological condition, influenced by swimming of the fetus. It becomes pathological when: (1) the loop becomes tight, with grooving of the soft parts, as in Fig. 8, (2) the number of loops is increased, (3) it is accompanied by knots, (4) the head or extremity passes through the loop. The protective jelly of Wharton serves to insulate the vessels to a certain extent, otherwise looping would be a more

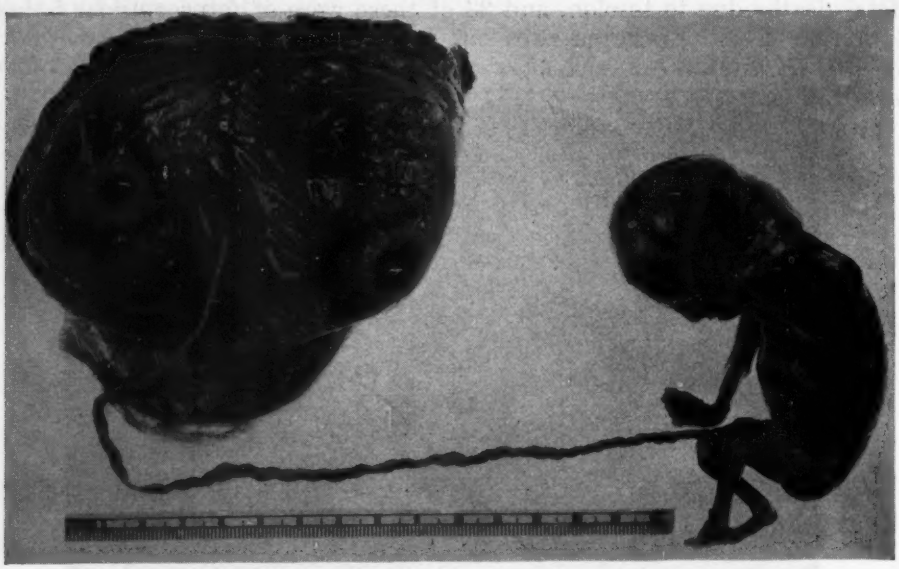

Fig. 5.—Very long cord of an abortus which measured 35 cm., while the crown-rump length of the fetus is only 10 cm. Torsion is also present with 40 distinct twists, some of which are evident in the illustration.

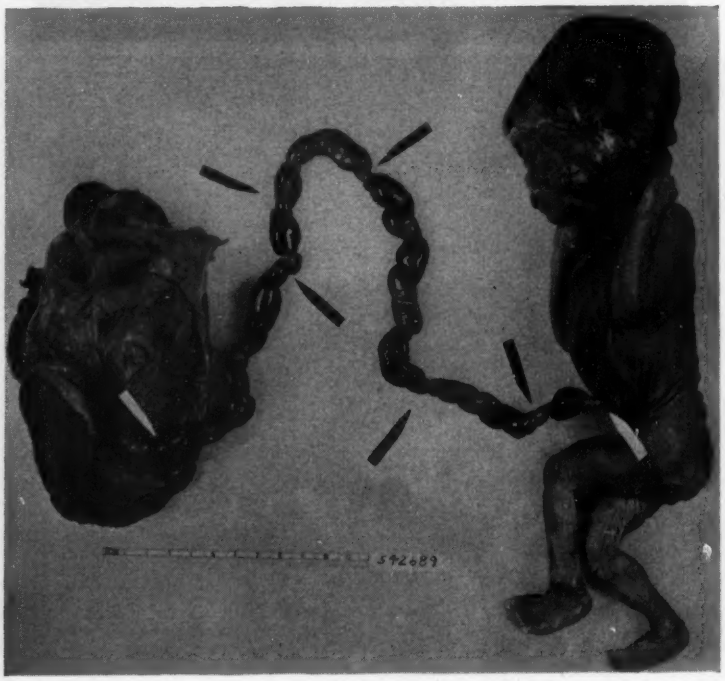

Fig. 6.—Segmental torsion of cord at seven different areas indicated by arrows. Fetus was macerated, gestation, 4½ months.

Fig. 7.—Torsion of cord at fetal end. There was an associated area of congenital atresia, or "coarctation" of cord, as in Fig. 8. The twist occurred at the squamous-amniotic junction of the cord. Fetus weighed 400 grams.

Fig. 8.—Simple loop around neck, tight enough to groove the soft tissues, and strangulate the infant.

Fig. 9.—Multiple looping of a very long cord, around the neck 3 times, twice around the shoulder and partly around arm, causing fetal death.

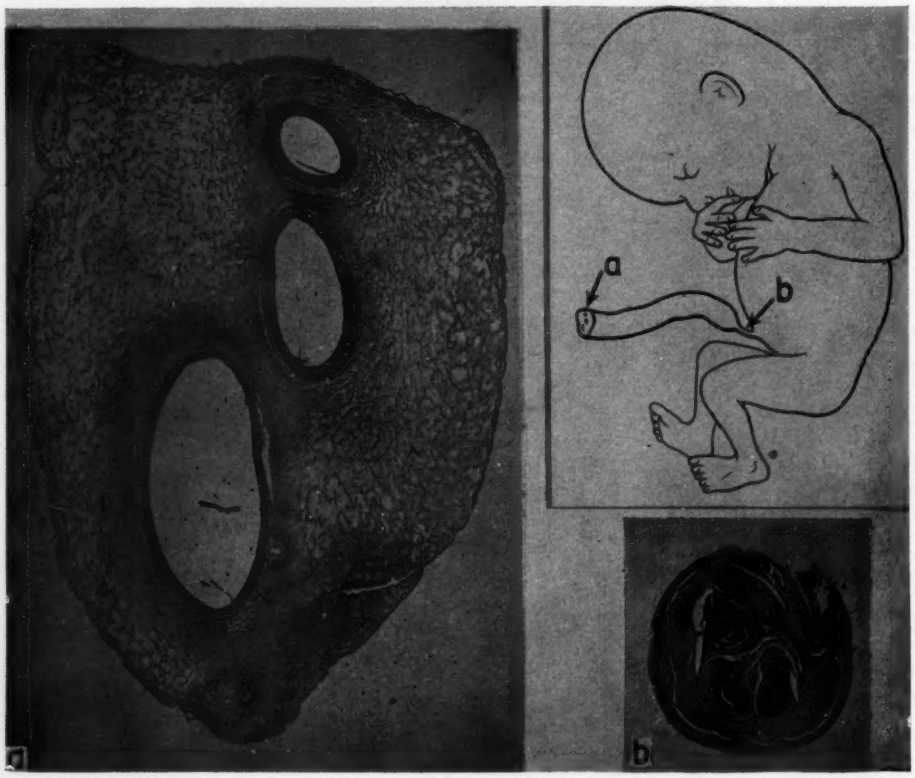

Fig. 10.—Diagram of coarctation of cord at fetal end. Low-power photomicrograph of *a* reveals normal portion of cord, while *b* shows the constricted end, with marked reduction of the caliber of the fetal vessels. Same magnification for both *a* and *b*.

Fig. 11.—Looping and overhand knot around knee, which was deeply grooved. Fetus was one of twins and partly mummified. Other twin was normal and so was the cord.

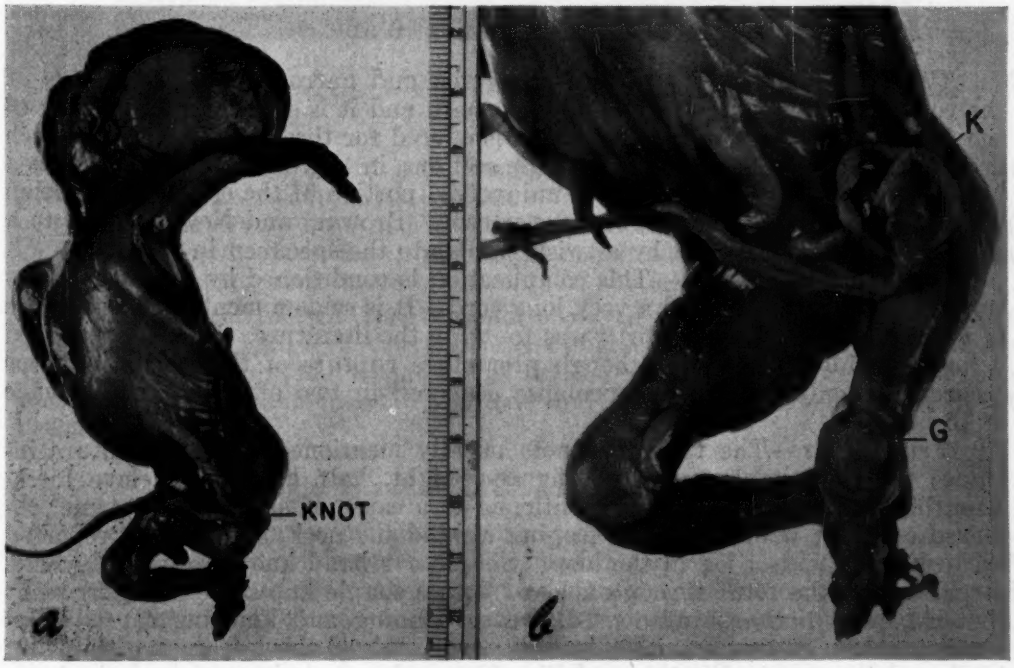

Fig. 12.—True knot around knee, in *a*, while, in *b*, the knot has been removed to show grooving at *G*.

frequent cause of intrauterine death. As many as 8 loops have been reported around the neck, and Fig. 9 shows a very long cord with 3 loops around the neck, and 2 around the shoulder.

Looping was observed in 6 cases, or 5.7 per cent. Hertig and Edwards[2] report an incidence of only 0.5 per cent in 219 conceptuses. It was usually around the neck, although in two cases it involved the knee. Pigeaud[12] noted 14 cases in 110 specimens, 6 around the neck, 6 involving the extremities, and 2 around the shoulder.

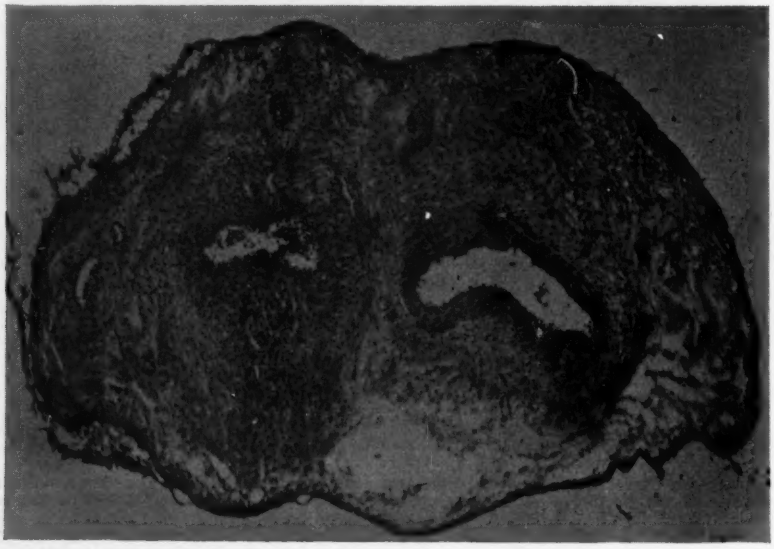

Fig. 13.—Vascular anomaly of cord. Section revealed one artery and one vein. Gestation, 4 months, "missed abortion."

Coarctation of Cord.—Stricture, atresia, and narrowing of the vessels of the cord may occur anywhere along its length and it is seen most frequently at the fetal end. The term "coarctation" is offered for these lesions, two of which are shown in Figs. 7 and 10. Histologic sections, in Fig. 10, reveal the narrowed blood vessels, as compared with an uninvolved portion of the cord. Coarctation has been observed in 9 cases, or 8.6 per cent. Browne[3] and Novak[11] refer to a similar lesion accompanied by a twist, similar to the specimen in Fig. 7.

Prolapse of the Cord.—This complication is conditioned by premature rupture of the membranes, and a very long cord. It is seldom mentioned as a cause of abortion and only one report[15] was found in the literature. We have observed 2 cases, or 1.9 per cent. Although premature rupture of the membranes was recorded in only 12 patients, prolapse occurred in two of these, an incidence of 16 per cent.

True Knots.—The types of knots usually mentioned in the literature include: true or simple overhand, figure-of-eight, half hitch, and clove hitch. Knotting of the cord is seldom mentioned as a cause of abortion. Browne[3] observed one case with associated looping around the neck, and Jaede[16] reported a clove hitch, with a leg in the loop. Simple overhand knots are probably due to passage of the fetus through a loop. Loose simple knots are not infrequent at term, with liveborn infants. However, looping and knotting caused fetal death in utero of two previable infants; one involved the left knee with a half hitch and loop, as in Fig. 11, and Fig. 12 reveals a true knot around the knee. In each case the soft parts were deeply grooved, and both fetuses were partly mummified.

Edema of the Cord.—Edema is usually found in association with a vascular obstruction secondary to looping, torsion, or atresia. Primary edema was observed in only one case and no apparent cause was discovered.

Vascular Anomalies.—The umbilical cord is usually regarded as having two arteries and one vein. Whittaker[18] mentions two arteries and two veins in early gestation, which we have not observed. Branching and kinking of the vessels are not uncommon, so that, on occasion, cross section of the cord may reveal six or more vessels.

Vascular anomalies were seen in only one cord; it had an artery missing (Fig. 13). However, this lesion has been seen in normal infants, delivered at term, so that its full significance remains unknown.

Fig. 14.—Placenta of a twin pregnancy delivered at term, showing one twin weighing 65 grams in its membranes, and no evidence of a cord. The larger placenta is of the twin born alive at term.

Twin Pregnancy.—Cord complications occurred in one each of two twin pregnancies. One case has already been referred to above, under "True Knots" of the cord, as can be seen in Fig. 11. The other specimen had no evidence of an umbilical cord. It is shown within the membranes in Fig. 14, together with the placenta, along with the term placenta of the other twin who went to term.

Entanglement of twin cord was not observed in this series although it has been observed by Quigley,[7] who collected 109 cases, of which 24 were nonviable and therefore within the scope of this article. Sonntag[19] reports 16 abortion specimens with entanglement and Boyle and Richter[21] observed a case at 34 weeks' gestation.

Pathologic Fetuses and Abnormal Cord Conditions

The role of the abnormal fetus as an etiological factor in spontaneous abortion has been shown by the works of Mall and Meyer[1] and Hertig and Edwards.[2] Their classification of the pathological fetus has been followed in this study and includes: the absent fetus, empty chorion, agenesis, the amorphous, cylindric, nodular, and stunted embryos, and fetuses with congenital malformations. Macerated, degenerated, and mummified fetuses, without other abnormalities, were placed in a separate group, as demonstrated in Table IV. These authors studied selected material often sent to them because of the obvious pathology;

while our study of 380 cases was less selective, it was based on the fact that tissue specimens from consecutive patients were sent to the pathological laboratory. The incidence of pathological fetuses was 24 per cent, in this material, a figure somewhat lower than reported by the previously mentioned authors, as shown in Table III.

TABLE III. INCIDENCE OF PATHOLOGICAL AND MACERATED FETUSES IN SPONTANEOUS ABORTIONS

AUTHOR	YEAR	TOTAL NUMBER OF CASES	FETUSES INCIDENCE IN PER CENT	
			PATHOLOGICAL	MACERATED
Mall and Meyer	1921	1,000	31	
Hertig and Edwards	1940	1,027	47	27
Javert and Barton	1951	1,000	24	50

TABLE IV. INCIDENCE OF CORD LESIONS IN SPONTANEOUS ABORTION SPECIMENS WHEN THE FETUSES WERE NORMAL AND ABNORMAL

FETUSES	NUMBER OF CASES	ABNORMAL CORDS	
		NUMBER	PER CENT
Normal (control)	98	6	6.1
Abnormal			
Pathological*	91	51	56.0
Macerated, degenerated, and mummified	191	47	24.6
Total	380	98	34.7

*Including: absent fetus, agenesis, amorphous, cylindric, nodular, and stunted embryos, and those with congenital malformations.

Comparison of data in Tables I, III, and IV reveals that abnormal conditions of the umbilical cord have a higher incidence (35 per cent) than the pathological fetuses (24 per cent). Table IV also reveals an incidence of cord complications of 25 per cent for the macerated fetuses and of 56 per cent in the pathological group. This is in sharp contrast to the lower incidence of only 6 per cent when the fetus was normal. To be sure, 50 per cent of the cords were found to be absent when the membranes were intact. Nevertheless, if this group were eliminated completely, abnormal conditions of the cord would still have a high incidence of around 17 per cent.

It would appear from personal experience with 1,000 specimens, that many of the so-called pathological fetuses are the result of cord complications and are, therefore, not the factor per se which precipitated the spontaneous abortion.

Conclusions

1. A study of 1,000 consecutive spontaneous abortion specimens submitted to the pathological laboratory yielded 297 cases with umbilical cords sufficiently complete for gross and/or microscopic analysis. Of this number, 104, or 35 per cent, were abnormal, in contrast to 4.8 per cent in a control group of therapeutic and unintentional abortions.

2. The lesions observed in the cord can be divided into two groups: (a) congenital, including: achordia without fetus, very long, very short, coarctation, and vascular anomalies, (b) acquired: achordia with embryo, excessive torsion, knotting, looping, prolapse, and edema. Other conditions, such as entanglement, varicosities, hematomas, cysts, tumors, thrombosis, spontaneous amputation, and the split cord, were not observed in this series.

3. Approximately 64 per cent of the lesions were congenital and 36 per cent were acquired. However, multiple lesions, i.e., very long cord and looping, occurred in 13.4 per cent of the cases.

4. The percentage incidence of each lesion was as follows: Achordia without fetus, in 41 per cent; achordia with fetus, in 8.6 per cent; very short cord, in 2.8 per cent; very long cord in 10.5; excessive torsion in 15.3; looping in 5.7; coarctation in 8.6; prolapse and twin pregnancy with abnormal conditions of cord in 1.9 per cent; vascular anomaly, true knot, and edema each in 0.9 per cent.

5. Most of the cord complications were such as to compromise the fetal circulation, so as to cause death in utero. Clinically, the resulting abortion began as a "missed" abortion. A flurry of fetal movement followed by a loss of activity may permit diagnosis of a cord complication.

6. There were 380 fetuses complete enough for evaluation of their abnormal and normal status, in the total material, of which 91, or 24 per cent, were pathological. This incidence is somewhat less than that of 35 per cent for abnormal conditions of the cord. Therefore, it would appear that the abnormal cord exceeds the pathological fetus as an etiological cause of abortion.

7. The incidence of cord lesions was 56 per cent in the total number of pathological fetuses, indicating the abnormal cord as an important associated cause of the "pathological" fetus. Macerated, degenerated, and mummified fetuses had cord complications in 24 per cent. These percentages are in sharp contrast to an incidence of only 6 per cent when the fetus is normal.

Appreciation is due Miss Barbara Turkington for the excellent photography, Dr. William H. Cary for suggesting the term "achordia," and Dr. William Sweeney for the word "coarctation."

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RUPTURE OF THE BASAL (DECIDUAL) PLATE IN ABRUPTIO PLACENTAE: A PATHWAY OF AUTOEXTRACTION FROM THE DECIDUA INTO THE MATERNAL CIRCULATION

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THE present purpose is to investigate the possibility of a pathway that may permit return of blood from the retroplacental hematoma of abruptio placentae, back into the maternal circulation. Interest in such a pathway lies in the possibility that this may permit rapid release of active substances from the decidua into the maternal circulation.

In the uteroplacental lesion of "accidental hemorrhage" (abruptio placentae) a retroplacental hematoma is formed and coagulates in situ so that its relation to the subtending placental tissues can frequently be studied from the delivered placenta. This was described by Young[36] in 1914; his findings and the probable intradecidual positions of the hematomas are readily confirmed.[19, 22] Microscopically, focal degeneration of the decidua has been described,[7, 36] and this has been attributed to atheromas of decidual arterioles.[7] The present investigation, although also concerned with the relationships of the placenta to the hematoma, is concerned primarily with neither of these aaspects, i.e., neither with the grossly visible relationships nor with the minute histology of the decidua, but rather with an intermediate scale of anatomic organization, in particular with a rupture, or spontaneous laceration of the decidual plate of the placenta.

For this investigation, a selected portion of a hematoma in situ on each of two selected placentas was studied. In each, a laceration of the basal plate was found and the margins of the laceration gaped by several millimeters. As can be seen in Figs. 2-10, sections of considerable size were prepared. This permitted evaluation of the anatomic relationships of the laceration. From the figures it can be seen that the laceration created a free communication from the intradecidual space of the hematoma into the maternal lake of the placenta.

Methods and Observations

The first specimen was from the placenta of a patient with eclampsia. This was a 2 cm. retroplacental hematoma, i.e., a partial or self-limiting abruptio placentae. A section through the entire hematoma was studied (Figs. 2-6). The second placenta was from a case of clinically recognized abruptio placentae; there was an extensive retroplacental hematoma. An in situ portion of the hematoma was selected for study (Figs. 7-10).

Self-limiting abruptio: L. C. (HKH 109110). The case history and placenta are described elsewhere.[22] The patient was admitted because of severe pre-eclampsia during her third pregnancy. She had a single convulsive seizure after admission. The placenta was obtained at vaginal delivery eight hours

later. The baby survived. The blood of parturition was wiped off the placenta in order to inspect the basal plate more closely. In addition to numerous central and peripheral placental infarcts, and a single, older, retro- and intraplacental hematoma, there was also a quite *recent* retroplacental hematoma. This was visible on topical examination but was not conspicuous.[22] When narrow strips of the placenta were cut in a manner recommended elsewhere[1, 36] the retroplacental hematoma was of striking appearance (Fig. 2).

Tissue sections from an entire sagittal plane of the hematoma, cut from the formalin-fixed, paraffin-embedded tissue, were stained with hematoxylin and eosin. The gross appearance of the hematoma in situ in such a section is shown in Fig. 3. This hematoma is intradecidual[22] as can be seen at higher magnification of the marginal portion of it (Fig. 6).

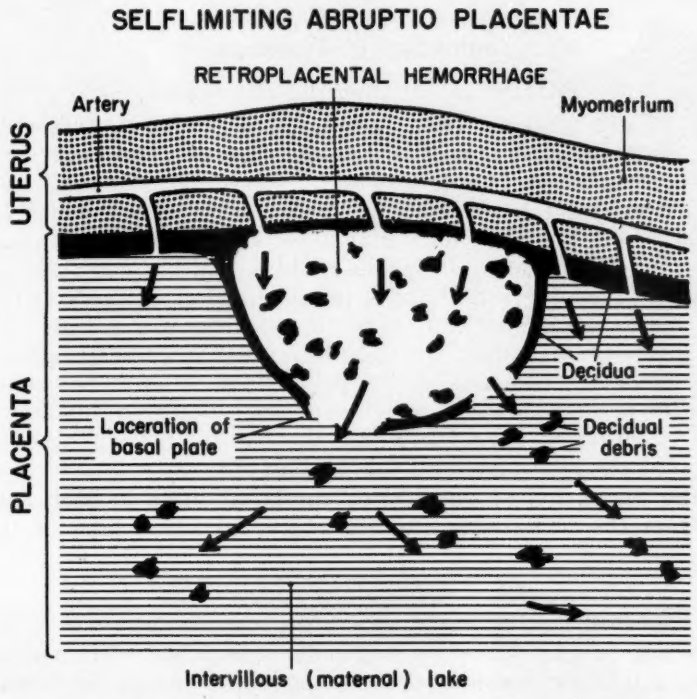

Fig. 1.—Schema of autoextraction of tissue substances, including thromboplastin, from the decidua into the maternal circulation. Hemorrhage of abruptio placentae is initiated spontaneously within the degenerating decidua. There results a mixture (extraction mixture) of decidual debris and tissue juices into the blood of the hematoma. The differential diameters of the hematoma and of the bleeding arterial sinusoids are such as to result in an expanding force within the hematoma (see text). The force results in a laceration of the frail, confining wall of the basal plate. As a result, the extraction mixture escapes into the maternal or intervillous lake of the placenta. From there the extracted materials may become dispersed throughout the general maternal circulation. Complications may result including "fibrin embolism" because of initiation of coagulation within the circulating blood. Modified after Schneider.[19]

The hematoma is enclosed by and is restricted from the maternal lake of the placenta only by the basal plate (Figs. 3-6). This basal plate is made up of the usual split thickness of decidua basalis, layer of trophoblast and "fibrinoid" (Nitabuch's and Rohr's layers), the basal plate being developed to an unusual thickness (Figs. 3-6). Chief interest lies not in the continuity of this enclosing basal plate, but rather in a laceration of it. The margins of the laceration (Figs. 3-5) gaped by 0.5 cm. in the axis that was studied.

Complete abruptio: C. P. (HKH 112395). This patient, while in the third trimester of her third pregnancy, developed clinically recognizable abruptio placentae. The symptoms and signs became prominent during labor and were classical; she had a painful, tense, and

tender uterus, and went into moderate shock. There was marked vaginal bleeding. No blood fibrinogen concentrations or other special determinations were carried out. The 1,800-gram fetus was stillborn. The placenta was accompanied by large, firm, dark red clots. Upon slow transfusion of 1 L. of blood, which was less than the estimated blood loss, her blood pressure rose to 180/100.

There were adherent portions of a massive retroplacental hematoma on the maternal surface of the delivered placenta. This hematoma had apparently extended beneath all of the basal plate except for a narrow crescent-shaped margin of the placenta. There was a sharp "craterlike" transition between the crescent of the placenta that remained of normal thickness and the adjacent portion which was compressed behind the hematoma (Fig. 7). Tissue sections were cut from this transition region. The basal plate was found to be interrupted by a laceration, the margins of which (Figs. 8, 9, 10) gaped by 0.5 cm. in the axis that was studied.

Summary of Findings

Laceration of the Basal Plate in Abruptio Placentae.—

Figs. 3 to 10 demonstrate that a laceration of the basal plate of the placenta may occur in abruptio placentae and that the resulting aperture may be of considerable size.

It does not necessarily follow that similar lacerations could be found in any given portion of the basal plate that is in relation to a retroplacental hematoma, nor does it follow that a laceration could be found in the placenta of every case of abruptio placentae. Although, in the present instances, the regions to be examined were *pre*selected and both of the lacerations were several millimeters wide, yet demonstration of them was not possible by gross inspection and it was necessary to resort to *microscopic* examination. The selection of the section of tissue to be examined microscopically was accomplished by seeking out by gross examination a region where the basal plate was distended by the local expansion of the retroplacental hematoma.

Clearly the laceration or rupture of the basal plate in each case created a passageway from the hematoma into the maternal blood lake of the placenta.

Comment

A. Abruptio Placentae.—

Pathways out of the retroplacental hematomas, other than the lacerations observed here, might be considered. Among these would be passage through the terminal segments of decidual arteriolees or sinusoids which have become truncated by the premature placental separation.[19] Whether these would serve as effective passageways has yet to be investigated.

The lacerations demonstrated here probably could permit flow out of the hematoma for a short time only because these apertures like any others would

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Figs. 2-6.—*Self-limiting* retroplacental hematoma, such as is frequently associated with eclampsia.[22, 27, 36] The hematoma is in effect a congealed model of an early stage of abruptio placentae. It is the anatomic counterpart of the schematic diagram of Fig. 1.

Fig. 2.—Cross section of a fresh specimen of a placenta and its retroplacental hematoma in situ. One-half normal size.

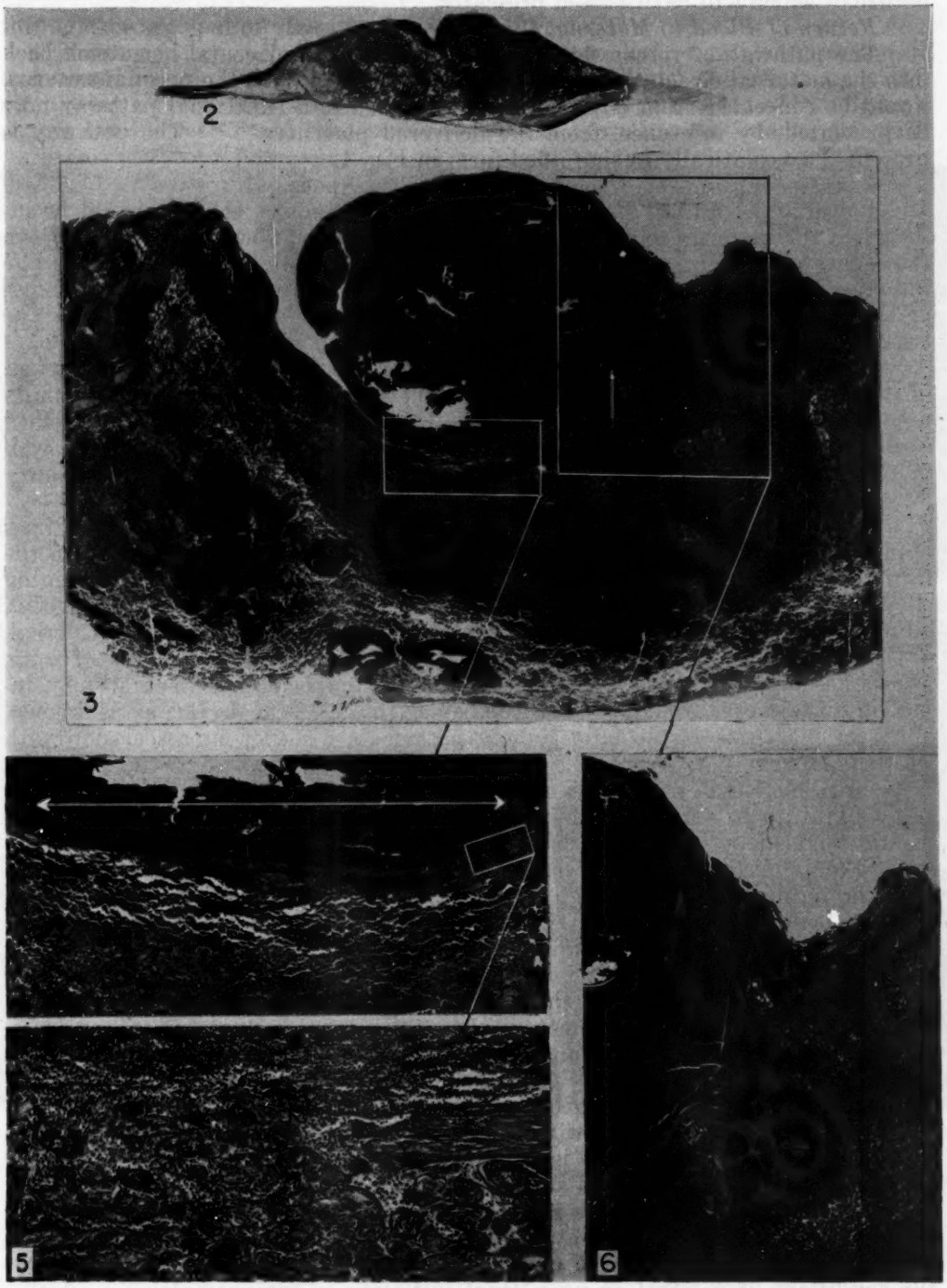
Fig. 3.—Appearance of the retroplacental hematoma of Fig. 2 in tissue section, twice normal size. Expansion of the hematoma appears to have compressed the subtending placental tissue. The hematoma is separated from the intervillous or maternal lake only by the basal plate of the placenta.

Fig. 4.—Enlargement of area of laceration of the basal plate. The actual separation of the two margins of the laceration, 5 mm., is indicated by the arrow.

Fig. 5.—Further enlargement, showing greater detail of one margin of the laceration.

Fig. 6.—Enlargement of a lateral aspect of the hematoma of Fig. 3, confirming that the hematoma is intradecidual. A margin of the decidua from the uterine aspect has come away with the hematoma. The hematoma is seen to be situated between this split layer of decidua and its opposite split portion on the basal plate of the placenta. The lateral intradecidual structures that limited further progress of the separation in this direction can be seen.

soon become closed by coagulation. The same coagulation that closed this escape route in the specimens studied preserved the anatomic form of the hematomas and of the passageways, thereby making the present study possible.



(For legends, see opposite page.)

The coagulation of these hematomas is *outside* of the circulation and is comparable to that in any hematoma. The coagulation within this extravasation is to be distinguished temporally, spacially, and in histologic pattern of fibrin deposition from another kind of coagulation, *within* the circulation, the nature of which will be discussed presently.

Return of Blood to Maternal Circulation.—

The pathway of return flow of blood from a retroplacental hematoma back into the maternal circulation, while still functioning within the pregnant uterus, would be concealed from observation. Nevertheless, a functional pathway may be presented, by inference, from the delivered placentas.[19, 22] The pathway is presented schematically in simplified form in Fig. 1.

Effects of Passage of Blood Through a Tissue Space.—

It would be difficult to anticipate how many kinds of changes might be induced in the maternal blood if even a small amount of it were to pass through the separated decidua and return to the circulation, as indicated in Fig. 1. The influences secondarily elsewhere in the body could conceivably be far reaching, and the ultimate consequences upon antigenic, toxic, hemolytic, hemostatic, or other mechanisms, perhaps, extensive.

It is possible that there could be considerable effects from simple contact of the blood with the "foreign surface" of the exposed decidual tissue, especially upon the coagulation mechanism. A similar kind of "foreign surface" effect could perhaps be anticipated in that type of dissecting aneurysm of the wall of the aorta, in which the blood finds a passage back into the aorta at a lower level and thus again into the general circulation.

By contrast, closely associated with abruptio placentae, there sometimes appears to have occurred a still more direct and overwhelming effect upon the initiation of coagulation within the circulating blood.[18, 19, 20] The fibrin plugging observed in fatal human abruptio placentae[20] is comparable to that resulting either from experimental abruptio[18] or from the intravascular injection of lethal, or near lethal, doses of agents of coagulation.[18, 19, 21] While this kind of acute disseminated, intravascular coagulation can be induced experimentally by injection of either thrombin[8] or thromboplastin,[18, 19] yet, so far as is known, abruptio placentae is the only human pathologic disorder in association with which it occurs.

From histologic examination it is concluded that the characteristic fibrin plugs build up in situ.[18, 19] This appears to be the result of a process of incremental fibrin deposition which may be referred to as "fibrin embolism."[20]

"Fibrin Embolism," a Morbid, Intravascular, Coagulative Process.—

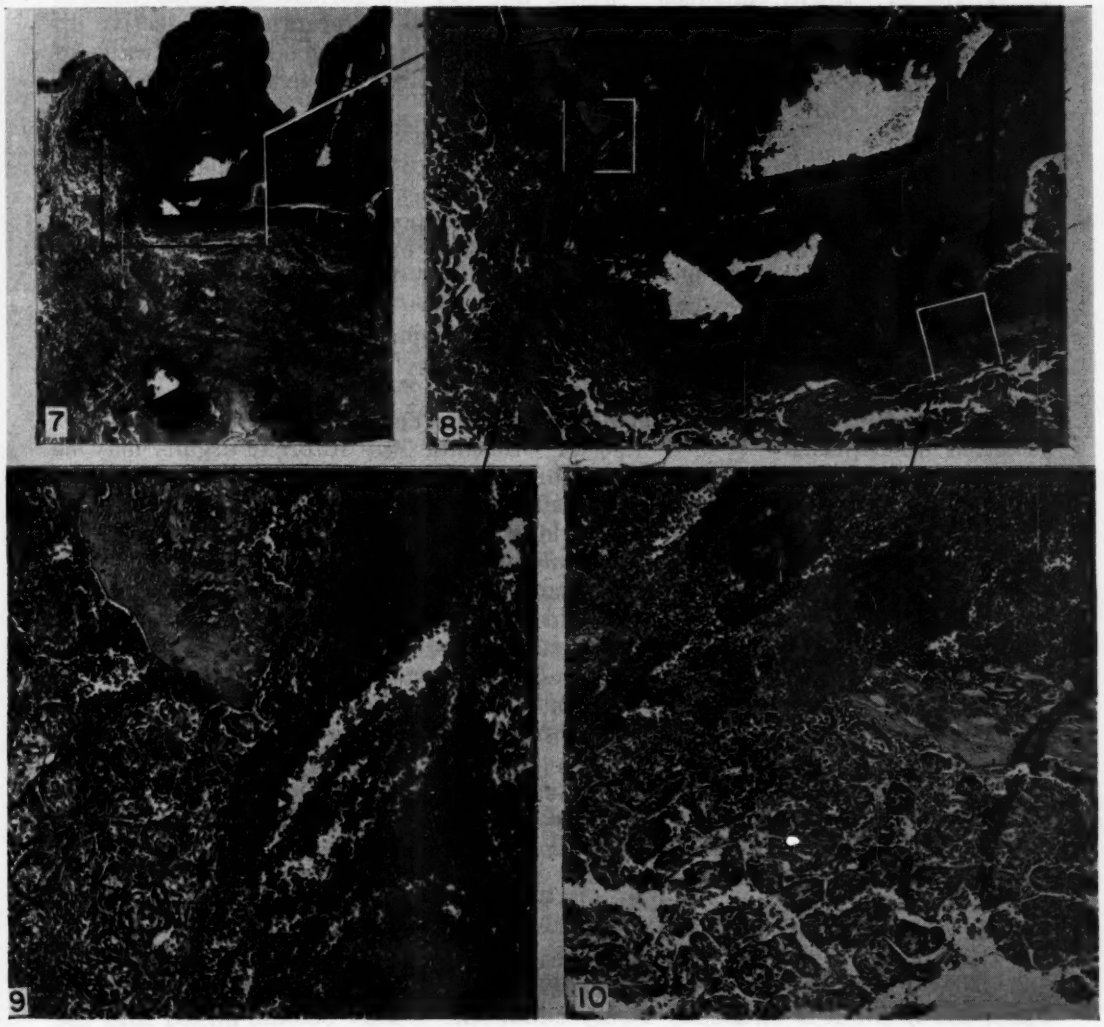
The nature of the process of "fibrin embolism"[20] is inferred largely from the histologic structure of the typical "fibrin plugs" and from the knowledge that the fibrin deposition is induced almost instantaneously by disseminated intravascular coagulation. The coagulation may have been induced deliberately by intravascular injection of thromboplastin,[17, 18, 19] by inducing tissue autoextraction in a kind of experimental abruptio placentae,[18] or spontaneously by the autoextraction of thromboplastin from the decidua during human abruptio placentae.[19, 20]

The process of "fibrin embolism" has thus far attracted only minimal attention as a subject of study within the living individual[11, 14, 17, 33]; interpretation of the process at present is based upon resultant changes, or aftereffects, still visible in tissues fixed and stained for microscopic examination.[20]

The histologic observations are that even after an ordinary, overwhelmingly massive, and disseminated intravascular coagulation, coagulation of whole blood as such is not found; i.e., the coagulum that is formed intravascularly under the conditions of a lethal or near-lethal initiation of intravascular coagulation is not comparable to the coagulum of whole blood formed while at rest in a test

tube. The fibrin deposit fills the lumen of the (contracted) vessel. The fibrin appears to be deposited out or "whipped out"[24, 25] differentially with a paucity of formed elements and with the internal structural pattern of a dense cable of fibrin.[18, 19] In this peculiar and characteristic "fibrin plug" the individual fibrin fibrils are oriented parallel to each other in the lines of flow of the blood through the segment of vessel under observation.

Wide variation may be induced by varying the dose or rate of injection of the agent inducing the coagulation.[8, 18, 19, 20, 21, 33] When the effect upon the circulating blood is observed microscopically in vivo, a gross kind of "sludging" can be seen,[11, 14, 17, 33] and the sizes of the masses as well as the interference with



Figs. 7-10.—Severe or complete abruptio placentae. The gross lesion is characteristic of many cases of clinically severe abruptio placentae. This congealed portion of the gross specimen is the anatomic counterpart of a lateral aspect, at an advanced stage, of the diagrammatic lesion of Fig. 1.

Fig. 7.—Full thickness of placenta showing transition zone at one border of the retroplacental hematoma and demonstrating compression of the subtending placental tissue. Photograph of tissue section, twice normal size.

Fig. 8.—Enlargement to show zone of laceration of the basal plate. The actual distance between the two margins of the laceration (distance between the two squares) is over 5 mm.

Figs. 9 and 10.—Further enlargement showing detail of the margins of the laceration of the basal plate.

the circulation increase sharply with the dose.[17] So also do the histologic structure[18, 19] and the content of formed elements within the fibrin plugs.[17, 21] Minimally effective doses of thromboplastin result in an excessive burden of leukocytes within the pulmonary arterial fibrin plugs[21] such that these may have the appearance of "white cell thrombi"; at the other extreme, massively supralethal doses result in grossly visible coagulation even of the blood within the great veins.[17] This wide range of type of intravascular plugging is mentioned here merely for the sake of completeness; it is noteworthy that, although these variations may at times obscure the underlying process of "fibrin embolism," this process appears still to provide the basic structure of the occlusions.

Steps in "fibrin embolism" would be: (1) the formation of myriads of minute fibrils within the circulating blood, (2) the differential or selective attachment of these fibrin threads from the circulating blood, to the walls of susceptible vessels, and (3) orientation of these fibrils in the vascular axis during the process of deposition.[20]

It becomes evident that this process is peculiar in that the fibrin plugs are built up in situ, in that the essential deposits are built up by increments of fibrin rather than of platelets, in that the embolism appears to be one of fibrin increments and not of masses (detached, embolic, composite masses are at times observed), in that the coagulation is not localized, but disseminated throughout the circulation, in that the fibrin deposition is not upon damaged intima but is built up on intact and healthy intima, and in that the fibrin deposition occurs not predominantly in the peripheral venous system, but also and perhaps predominantly as an arterial deposition. A favored site of deposition appears to be in the pulmonary arterial circulation.[18, 19, 20] The deposits also occur elsewhere, including the renal glomerular afferent arterioles and capillaries.[1, 20] If recorded descriptions[1, 4, 15, 20, 26, 28, 30] of "thrombi" in different organs may be interpreted,[20] even in part, as being fibrin plugs of this type, then additional favored sites might well be the "portal" systems, notably the portal system of the liver, but also that in the pituitary gland.

The apparent process of fibrin embolism depends upon a rapid and disseminated initiation of intravascular coagulation.[19] Sufficiently rapid initiation of coagulation within the circulating blood can be brought about spontaneously only by an active autoextraction of tissue substance into the maternal circulation.[19]

Autoextraction of Decidual Substance.—

The decidua at the locus of a retroplacental hematoma has been described[7] as degenerating or necrotic. In such an environment, if not also within a separation of normal decidua of the third trimester, tissue juices and tissue debris would be prone to become mixed into the blood of the hematoma.[19] If the blood of the hematoma then escaped back into the circulation, it could have served as the extracting medium, as a vehicle, in an autoextraction of tissue substances into the general circulation[19, 21] (Fig. 1).

Autoextraction of Thromboplastin.—

Of immediate interest it may be concluded that, as a result of autoextraction of decidual tissue substances, effectively large doses of thromboplastin, with which the decidua is unusually richly endowed,[16-19] may become mixed into the maternal blood stream during abruptio placentae.[18, 19, 20] Support is lent to this conclusion by the "bridging" experiment of "experimental abruptio" in the pregnant rabbit.[18]

In the experimental abruptio,[18] the conclusion that there is an immediate disseminated coagulation initiated by substances of decidual-tissue origin rests upon the pathologic observations. Not only could there be immediate maternal death with the characteristic, disseminated, pulmonary, intra-arterial "fibrin plugs," but, at the same time, embedded within these fibrin plugs were recog-

nizable decidual tissue elements. The tissue elements were multinucleated cells, probably from the degenerating portions of the maternal placenta (the maternal portion of the placenta in the rabbit is of considerable thickness and undergoes extensive degeneration near term[13]). That these trophoblast cells were not merely deportations incidental to pregnancy, but were released into the maternal circulation at the time of the fibrin deposition (the time of placental trauma) was evident from the scattered distribution and embedding of them within the acute and lethal intra-arterial fibrin deposits.

Mechanism of Autoextraction.—

It may be enquired whether an active force would be a prerequisite for sufficiently rapid autoextraction to provide a "toxic" level of thromboplastin.[19] By contrast, a rapid build-up of the blood level may not be required of other endometrial[29, 31] or placental[1, 2, 29] "toxins," in order to produce even a lethal pathologic result. It is because of the apparent requirement of a rapid release into the circulation that an active autoextraction has been postulated in abruptio placentae[19] and it is possible that a unidirectional force for this may be provided within the hematoma by the very nature of the maternal blood supply to the placenta.[19-22]

The maternal arterial blood supply to the placenta, as revealed by the injection and corrosion experiments of Spanner,[32] is transmitted throughout the decidua basalis. Through these retroplacental regions there is little or no venous drainage from the placenta; near term, the venous outflow is directed exclusively to the margins of the uteroplacental attachment.[32] It follows that any *retro*placental separation, i.e., any hematoma that separates off a cotyledon of the placenta from the uterine wall (but not the hematoma of a marginal separation, see below), is fed by an arterial supply. This is of significance in the expansion of a retroplacental hematoma.

The diameter of the hematoma chamber is considerably greater than the diameter of the arteriolar blood supply that feeds it. From these relative diameters it follows that the retroplacental hematoma may be in effect a hydraulic pump[19-22] in the sense of a force within a large-bore chamber (the hematoma) activated by a force from a smaller-bore chamber (the decidual arteriole). Such a hydraulic pump action would provide an expanding force for the hematoma. That considerable force may indeed develop is suggested by the compression of the subtending placental substance to half-thickness (Figs. 3, 7).

It is to this apparent expanding force that we may look for the cause of the laceration of the frail basal plate subtending the retroplacental hematoma (Figs. 2-10), and hence this is the force that seems to have opened an effective pathway of autoextraction from the hematoma into the maternal blood lake.

Progress of Placental Separation.—

In abruptio placentae, the duration of autoextraction[19-22] becomes a problem of considerable significance both theoretically and clinically. It is clear from inspection of Figs. 2-10 that coagulation of the extraction mixture within the hematoma chamber (Fig. 1) would soon bring the local extraction process to a halt by blockage of the outlets. At any locus of separation of the placenta, such coagulation may be presumed to occur within seconds or minutes after the separation.[22] However, the uteroplacental separation may extend in any of several directions, and thus momentarily, from time to time, renew the process. Evidence of gradual or stepwise extension occasionally can be observed clinically. For example, the continuous uterine tenseness and tenderness may give way to relative relaxation with simulation of conditions of labor, only to return later to a renewed bout of "boardlike" spasm, perhaps with associated shock.

Such bouts may continue over an interval of as much as half a day from the onset of symptoms of abruptio placentae until final disappearance of the fetal heart sounds (Case 3).[20]

It is not excluded that a similar mechanism of autoextraction may become significantly effective late in the second stage of labor (i.e., during delivery of the infant) or even, on rare occasions, during the third stage (i.e., during "normal" separation and delivery of the placenta). If decidual autoextraction did occur so late in labor, it is improbable that the conditions would be appropriate for formation and preservation of a congealed model of a retroplacental hematoma as in the cases considered here.

It is conceivable also that when a retroplacental hematoma extends to become a marginal hematoma as well, autoextraction could proceed for a time from the hematoma directly into the marginal sinus, and this could serve directly as a path of return into the maternal circulation. In effect this would be merely a special instance of abruptio placentae. A case with a self-limiting hematoma has been observed in which this may have occurred.[22]

Definition of Abruptio Placentae.—

From the foregoing discussion, the usual definition of abruptio placentae is confirmed and may be more precisely stated as: any premature separation of any normally implanted portion of the placenta; i.e., a separation beneath any cotyledon or cotyledons. Conversely, a marginal separation would not be classified as abruptio placentae.

B. Other Uteroplacental Separations.—

By comparison with the uteroplacental separation of abruptio placentae, other types of uteroplacental detachments are poorly adapted as a means of effective autoextraction because the hemorrhagic blood does not return to the circulation.

Placenta Previa.—

In this condition, most of the blood of the hemorrhage escapes from the body entirely, directly through the cervical os. This is indicated schematically in Fig. 11. Little, if any, of the escaping blood can serve as a vehicle for autoextraction because the blood does not return to the circulation.

Marginal Separation of the Placenta.—

In simple marginal separation (Fig. 13) the marginal hematoma would expand not under arterial pressure but under venous pressure, and this the venous pressure of the maternal lake. Since the inflow is from the maternal lake, the reverse direction, namely, backflow into the maternal lake, is not a likely avenue of escape. Direct outflow in the uterine direction, i.e., from the hematoma directly into the communicating marginal venous sinusoids of the uterine wall itself, while plausible, would more likely tend toward prompt compression and collapse of the transected sinusoids, and thus to occlusion of the outflow. Some degree of spontaneous dissection of the hematoma beneath the membranes and perhaps some escape of blood through the cervical os is the likely path of flow. It may be provisionally concluded that marginal separation, as a potential mechanism of autoextraction, lacks an efficient avenue for any considerable return flow into the maternal circulation.

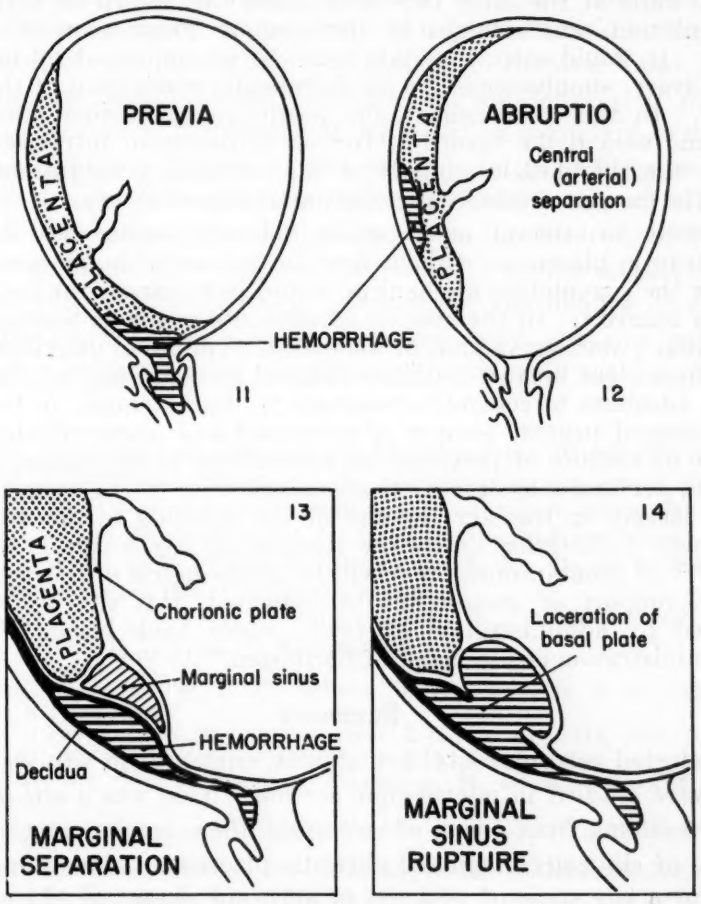
Rupture of the Marginal Sinus.—

In "rupture" of the marginal sinus, the rupture of the sinus usually occurs through the decidual surface, and not through the chorionic plate into the amniotic sac. Thereafter, the path of blood flow from the rupture becomes quite comparable to that from simple marginal separation (Fig. 14). Hence, although in extreme cases the external blood loss becomes alarmingly rapid clinically, this very hemorrhage would indicate that rupture of the marginal sinus is little or no better adapted to decidual autoextraction than is simple marginal separation.

That neither placenta previa nor marginal separation fulfills the anatomic requirements for active autoextraction is in agreement with the clinicopathologic differentiation of these conditions of "revealed hemorrhage" from abruptio placentae (Fish, Bartholomew, Colvin, and Grimes[5]). Clinically, the hemorrhage of marginal separation is usually mild and readily controlled by direct obstetrical management.[5, 27]

C. Deductions Concerning Therapy in Abruptio Placentae.—

The apparent risk of a tendency toward progression of the premature placental separation toward completion in cases of abruptio placentae leads to a suggestion of caution in therapy.[25] This is because during the progression of the separation there is an ever-present hazard of continued or renewed autoextraction. This in turn may lead to renewed, disseminated intravascular co-



Figs. 11-14.—Comparison of the hematoma formed in different uteroplacental separations. Only abruptio placentae is adapted to autoextraction. See text.

Fig. 11.—Placental previa. The hemmorrhage escapes through the cervix and therefore cannot serve as a vehicle of autoextraction.

Fig. 12.—Abruptio placentae. Because the hemorrhage is of arterial origin there is an expanding force. The likely path of escape of the hemorrhage is into the maternal lake, the blood thereby being returned to the maternal circulation. The blood of the hematoma may therefore serve as the vehicle for an autoextraction from the decidua. Compare with Fig. 1.

Fig. 13.—Simple marginal separation. Mild revealed bleeding is likely. Appreciable return of hemorrhage to maternal circulation is improbable, and hence autoextraction of significant degree unlikely.

Fig. 14.—Marginal sinus rupture. Revealed hemorrhage is more likely to be brisk. Mechanics of hemorrhage are similar to those of simple marginal separation, and poorly adapted to autoextraction.

agulation (see above) with attendant risks of added focal tissue damage[16, 17, 19] or of circulatory embarrassment[17, 21, 23] because of fibrin deposition within vital vessels. This may even become lethal.[20]

However, in rare but severe cases, wherein the patient with abruptio placentae has already undergone considerable depletion of fibrinogen[3, 4, 12, 14, 19, 20, 34, 35, 38] or wherein depletion has continued during observation of the patient,[20] a "hemorrhagic diathesis"[9, 10] may supervene, and therapeutic restoration of the circulating coagulation mechanism, either by transfusion of whole blood or plasma[3, 4, 9, 10, 14, 19, 20] or by infusion of fibrinogen preparations[12, 14, 34, 35] may seem to be desirable to support hemostasis.

In the severe cases (and any case of abruptio placentae is a potentially severe case), then, the problem may become one of restoring the coagulation mechanism while at the same time preventing the hazard of further intravascular coagulation, which might be initiated by progression of the placental separation. It would seem that this could be accomplished by bringing about prompt delivery, simultaneously with therapeutic restoration of the coagulation mechanism. In this management, the possibility of further autoextraction is removed, and with it the hazard of further initiation of intravascular coagulation, while the therapeutic support of the circulating coagulation mechanism minimizes the danger of hemorrhage during or after delivery.

Conversely, to attempt, or to permit, delivery, having once made the diagnosis of abruptio placentae, without first having available adequate therapeutic support for the coagulation mechanism, would be to expose the patient to potentially great hazard.[25] In the absence of adequate available therapeutic support of coagulation (whether vaginal or abdominal) operative interference would be extremely hazardous because ordinary surgical methods may not be, under these conditions, adequate to control hemorrhage.[20] For example, in the past, it has sometimes seemed urgent, because of continued and uncontrollable postpartum hemorrhage or because of postcesarean hemorrhage in association with abruptio placentae, to perform a hysterectomy secondarily.[4, 10, 20] This surgical procedure may serve merely to transfer the site of the bleeding to the uterine cervical stump[20] where it continues unless the coagulation mechanism is restored therapeutically[4, 20] or spontaneously as it will be in the course of a few hours. When therapeutic support of coagulation is indicated, this can probably be best accomplished by administration of fresh, whole bank blood,[14, 25] or, lacking this, by administration of plasma or of fibrinogen.[12, 14, 35, 36]

Summary

Two selected retroplacental hematomas, each still in situ on its delivered placenta, were studied in microscopic sections. One was a *self-limiting* retroplacental hematoma from a case of eclampsia, the other an extensive hematoma from a case of clinically diagnosed abruptio placentae. Thus these represented an early and a late stage of progress of abruptio placentae. In each the basal plate which otherwise separates the hematoma from communication with the maternal lake was found to be lacerated. These spontaneous lacerations appeared to be the result of an expanding force from within the hematoma itself.

It was inferred that at the time of spontaneous rupture of the basal plate blood from the hematoma may have returned through the laceration into the maternal lake, and thence back into the general circulation. It was further inferred that this provided a pathway for autoextraction of decidual tissue substances into the maternal circulation. A comparable mechanism of auto-

extraction during placenta previa, marginal separation of the placenta, or marginal sinus rupture seems improbable because a pathway for appreciable return flow to the maternal circulation is lacking.

The implications of the apparent decidual autoextraction, as an etiological factor in the acute maternal disorders of abruptio placentae, upon therapy are considered. It was reaffirmed that in abruptio placentae delivery usually should be accomplished promptly, even with resort to cesarean section if vaginal delivery is not imminent. This is to reduce the risk of further progress of the abruptio and of complications therefrom, including release of further activation of coagulation within the circulation. More importantly, whatever the obstetrical management, it becomes mandatory, once the clinical diagnosis of abruptio placentae is made, immediately to initiate "stand-by" preparations for restoration of the circulating coagulation mechanism (and blood loss). Need for this may become acutely manifest during delivery, if not before or after. This is because of the danger of defibrination secondary to intravascular coagulation, and failure thereby of hemostasis. Not to be prepared with large quantities of already cross-matched blood, or, lacking this, of other support of the circulating coagulation mechanism, is to run the risk of fatal hemorrhage from even minor lacerations of delivery or from the incisions of perineal or abdominal surgery for delivery. Because of the danger of extension of the premature placental separation, it is important that the restoration of the coagulation mechanism be simultaneous with, and not usually prior to, delivery.

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THE CAUSES OF FETAL MORTALITY AT THE SLOANE HOSPITAL FOR WOMEN, 1940 TO 1949

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IT HAS been obvious for some time that the fetal mortality rate on the private service at the Sloane Hospital for Women is considerably lower than the rate on the ward service. It seems desirable to discover the causes of this difference, so that further improvement in both rates might be made. For this purpose, a review of all of the antenatal and neonatal deaths at the Sloane Hospital for Women during the years 1940 to 1949 has been carried out. These deaths are made up of all stillbirths at twenty-eight weeks or later, and all live births, occurring at any time, which were followed by death within 30 days. The stillbirth rate is determined by calculating the ratio of the number of stillbirths at or after the twenty-eighth week to the number of births occurring at or after the twenty-eighth week, both stillborn and liveborn. The neonatal mortality rate is determined by calculating the ratio of the number of neonatal deaths occurring in infants born at or after the twenty-eighth week to the number of births occurring at or after the twenty-eighth week, whether stillborn or liveborn. Since both the stillbirth rate and the neonatal mortality rate are based on the same denominator they may be added directly to give the total fetal mortality rate. All rates are expressed in number *per thousand.* Those infants born alive before the twenty-eighth week and who subsequently died are calculated separately.

Material

During the decade 1940 to 1949, there were 12,327 private deliveries and 17,856 ward deliveries which occurred at or after the twenty-eighth week, at the Sloane Hospital for Women. In all, there were 486 stillbirths and 370 neonatal deaths, and these 856 cases form the material of this study.

Method

In each case it was desired to fix a primary cause of death from *the obstetrical point of view.* Pathological findings were always studied* but pathological terms as such were not used in the final classification, except where fetal disease alone was the sole cause of death. It was hoped that the resulting classification would point to specific causes of fetal deaths which could then be studied and either removed or improved upon. Therefore, in each case the mother's chart, the autopsy report, and the baby's chart when the baby lived were completely reviewed, and the cause of the fetal death was listed. In most cases, the cause was readily apparent. In some cases there was no cause to be found, so that a certain number are listed as "unknown." In a few cases the determination of the cause was made difficult by complex clinical factors, but

*The autopsy rate was 96.7 per cent on the ward service and 94.7 per cent on the private service.

TABLE I. FETAL MORTALITY RATES, WARD AND PRIVATE, BY YEARS, 1940-1949

	YEAR										
	1940	1941	1942	1943	1944	1945	1946	1947	1948	1949	TOTALS
Ward.—											
Deliveries	1,503	1,585	1,678	1,848	1,957	1,729	1,686	1,807	1,760	2,303	17,856
Stillbirths:											
Cases	22	29	48	44	40	35	34	37	20	53	362
Rate	14.6	18.3	29.6	23.8	20.4	20.2	20.2	20.4	11.4	23.0	20.2
Neonatal deaths:											
Cases	29	25	25	15	33	28	25	21	20	29	250
Rate	19.3	15.7	14.9	8.2	16.9	16.2	14.8	11.6	11.4	12.6	14.0
Total fetal mortality rate	33.9	34.0	44.5	32.0	37.3	36.4	35.0	32.0	22.8	35.6	34.2
Private.—											
Deliveries	965	1,031	1,074	1,046	1,079	1,269	1,593	1,513	1,372	1,385	12,327
Stillbirths:											
Cases	14	12	12	13	9	10	11	18	14	11	124
Rate	14.5	11.6	11.3	12.4	8.3	7.9	6.9	11.9	10.4	7.9	10.1
Neonatal deaths:											
Cases	10	11	10	11	7	20	15	13	10	13	120
Rate	10.4	10.6	9.3	10.5	6.5	15.8	9.4	11.7	7.3	9.4	9.7
Total fetal mortality rate	24.9	22.2	20.6	22.9	14.8	23.7	16.3	23.6	17.7	17.3	19.8

the number of these was small. The rates were then calculated for each year and for each service, and finally the stillbirth and neonatal mortality on each service were broken down into specific causes.

Results: Stillbirth and Neonatal Mortality Rates

The stillbirth and neonatal mortality rates from all causes for the decade 1940 to 1949 are shown in Table I, where it is seen that the ward stillbirth rate is 20.2 per thousand, and the private rate is 10.1 per thousand. The ward neonatal mortality rate is 14.0 per thousand and the private rate 9.7 per thousand. The total fetal mortality rates are thus 34.2 per thousand on the ward service and 19.8 per thousand on the private service. These figures (and all the data in this paper) have been subjected to statistical analysis, and the differences between ward and private services are found to be significant. There is, therefore, a valid difference between the two services which warrants study.

When the yearly figures are examined statistically, it is found that there is a very slight downward trend on each service. In no case, however, did this trend attain statistical significance. Whether this trend will continue and become statistically significant remains to be seen.

TABLE II. CAUSES OF FETAL MORTALITY (STILLBIRTHS PLUS NEONATAL DEATHS) ON WARD AND PRIVATE SERVICES, 1940-1949

		WARD			PRIVATE		
		STILL-BIRTHS	NEONATAL DEATHS	TOTAL FETAL MORTALITY	STILL-BIRTHS	NEONATAL DEATHS	TOTAL FETAL MORTALITY
Maternal disease	Cases	95	14	109	17	6	23
	Rate	5.3	0.8	6.1	1.4	0.5	1.9
Congenital defect	Cases	33	69	102	17	31	48
	Rate	1.8	3.9	5.7	1.4	2.5	3.9
Unknown	Cases	80	7	87	38	5	43
	Rate	4.5	0.4	4.9	3.1	0.4	3.5
Cord complications	Cases	65	12	77	22	3	25
	Rate	3.6	0.7	4.3	1.8	0.2	2.0
Prematurity*	Cases		68	68		39	39
	Rate		3.8	3.8		3.2	3.2
Birth trauma	Cases	38	27	65	10	10	20
	Rate	2.1	1.5	3.6	0.8	0.8	1.6
Fetal and neonatal diseases	Cases	20	31	51	4	10	14
	Rate	1.1	1.7	2.8	0.3	0.8	1.1
Premature separation of placenta	Cases	25	13	38	12	8	20
	Rate	1.4	0.7	2.1	1.0	0.6	1.6
Miscellaneous	Cases	7	3	10	2	2	4
	Rate	0.4	0.2	0.6	0.2	0.2	0.4
Placenta previa	Cases	3	6	9	0	6	6
	Rate	0.2	0.3	0.5	0	0.5	0.5

*Excluding births under 28 weeks.

The ward service has been divided into white and Negro, in an effort to discover the effect of race. The differences between the white and Negro groups are not statistically significant, and hence the valid difference between the ward and private services cannot be ascribed to the presence of Negro patients on the ward. The ward service, however, includes a considerable number of Puerto Ricans. These people are probably the poorest, economically and hygienically, of all the hospital patients. They exert a real influence on the ward rates, but because of the methods of listing patients on the charts this group cannot be separated as such. This group has been increasing in

numbers. The proportion of Negro patients on the ward service has also increased, from 19.3 per cent in 1940 to 45.4 per cent in 1949. On the private service the number of Negro and Puerto Rican patients is so small as to be insignificant. Hence there are marked racial variations between the two services, but these variations cannot be measured. The sources of the difference in fetal mortality between ward and private patients must therefore be sought among the various causes of fetal and neonatal mortality.

The causes of fetal and neonatal mortality, listed in the order of their frequency on the ward service, are shown in Table II. The variation of each cause was studied, and while there are variations from year to year, there is no clear trend for any of the causes.

1. Maternal Disease.—

This is the leading cause of fetal mortality on the ward service. In this category are those infants whose mothers had some serious medical complication of pregnancy, principally pre-eclampsia. Some of these infants died in utero during the course of the medical complication. Others were born alive but succumbed in the neonatal period. When delivery occurred before term in these patients (as by induction of labor, by cesarean section, or by spontaneous premature labor during severe pre-eclampsia) it was felt that although the neonatal death might well be *directly* due to prematurity the basic cause for the prematurity and hence for the fetal death should be classified *obstetrically* as the maternal disease. The distribution of these diseases during the entire ten-year period is shown in Table III.

TABLE III. MEDICAL COMPLICATIONS OF PREGNANCY ASSOCIATED WITH FETAL MORTALITY, 1940-1949

	WARD	PRIVATE
Pre-eclampsia	75	18
Hypertensive disease	20	1
Chronic nephritis	1	0
Diabetes	7	3
Syphilis	4	1
Severe anemia	1	0
Virus pneumonia	1	0
Total	109	23

The difference between the rates for the two services is statistically significant, so that this cause is responsible for fetal death three times as often on the ward as on the private service.

The cause for this difference appears to be the incidence of maternal diseases on the two services. The incidence of *all* medical complications on the ward service is four times that of the private service. The incidence of pre-eclampsia, hypertensive cardiovascular disease, chronic nephritis, and diabetes when grouped together is three times as great on the ward service as on the private service. Since the fetal loss from maternal disease is also three times as great on the ward as on the private service, it appears that there is a constant fetal risk from the diseases themselves, and the larger the number of cases treated the greater will be the number of infants lost.

Improvement in this category, then, will come with improved treatment, but, more important, with measures for prevention of these illnesses. The greater incidence of maternal disease on the ward service suggests that the economic status of the patient must exert some influence, and in addition the quality of the antenatal care on the private service must be better than on the ward service. In this respect, it must be noted that the Sloane Hospital for Women attracts patients with known disease or with a history of diffi-

culty in a previous pregnancy. Such patients are desired for teaching purposes and are admitted in preference to normal patients. This makes the incidence of various complications greater than in the entire population, and to some extent greater than on the private service, where these factors also operate but to a smaller degree.

2. Congenital Defects.—In this category are those infants, stillborn or who died in the neonatal period, with congenital defects incompatible with life. This cause is apparently responsible for a fetal mortality on the ward service about one and one-half times greater than that on the private service, but this difference is just on the border line of statistical significance.

The relation of parity to this cause was determined, and the ratio of primiparas to multiparas is found to be the same for those infants with congenital defects as in the entire group (primiparas: multiparas = 1:1 on the ward; 1.6:1 on the private service). The influence of age is not clear, in that these defects occurred in patients of all ages, and actually there are more of the older patients on the private service than on the ward service. Since congenital defects are said to appear more frequently in older patients, the private service would be expected to show more of these cases than the ward, but the opposite is true in this series. There is no significant difference according to race.

Since the factors of race, age, and parity cannot be shown to influence the incidence of congenital defects in this series, only speculation as to the cause of the difference between the ward and the private services can be offered. Congenital defects may in some instances be due to genetic factors, but in a group of patients as cosmopolitan as these, both ward and private, this factor ought to be nearly constant. On the other hand, it is possible that improper diet, or disease occurring during the early part of the pregnancy, may account for more congenital defects than do purely genetic factors. If this were true, economic status would exert a definite influence.

3. Unknown.—In this category are those cases in which no cause for fetal death could be determined, either in the fetus or the mother. Most of these were macerated stillborn infants where microscopic examination was impossible and gross examination failed to reveal congenital anomalies. A small number were cases in which the fetal heartbeat disappeared just before or during labor, and in which no defect of the placenta or cord could be found. This is an unsatisfactory grouping, but no other classification of these cases can be made. The difference between the two services is not statistically significant.

These cases are accidents of pregnancy and labor, and are probably not preventable in most instances. More detailed study just before or during the actual death of the fetus might demonstrate the cause, but this is not possible in most instances. Some cases are probably due to faulty function of the placenta, and others to defects in the child which are not demonstrable because of maceration, but unless and until practical methods of testing placental function are devised these cases will remain unsolved and nonpreventable.

4. Cord Complications.—In this group are placed those deaths attributable to interference with the circulation in the cord. There are three demonstrable situations in which this occurs: prolapse of the cord, the cord being seen or felt to be compressed; occult prolapse, the compression not being recognizable until after delivery; and cord around the body, usually the neck, drawn tightly enough to compress the cord. Some cases listed as "unknown" were probably due to this cause, but were excluded because the compression could not be demonstrated.

The difference between the two services is statistically significant. This means that the incidence of death from this cause is twice as great on the

ward service as on the private service. The incidence of prolapse of the cord (the only cord complication indexed) is approximately the same on the two services. This implies that this complication results in twice as many deaths on the ward as on the private service. The difference in fetal mortality is probably due to earlier recognition of the possibility of a cord complication and earlier treatment on the private service. The "chain of command" on the ward service sometimes results in delayed treatment.

5. Prematurity.—This is a cause of neonatal mortality only. In the method of compiling the neonatal mortality rate which we have used up to this point, only those infants born at or after 28 weeks are counted. By this method (Table II) prematurity is the second most common cause of neonatal death on the ward service and the first on the private service. The above ranking is considerably altered by including those infants born alive before 28 weeks who died in the neonatal period. There were 74 of these on the ward (37 white and 37 Negro) and 47 on the private service. When these are added to the deaths under prematurity appearing in Table II this cause becomes the largest single cause of death. There are then 142 deaths on the ward service and 86 on the private service, giving rates of 7.9 per thousand on the ward and 7.0 per thousand on the private service.

In this study, prematurity was listed as the cause of death only when no other cause could be found. Clinical prematurity was present in 49.2 per cent of all ward infant deaths and in 61.5 per cent of the private cases, and may have been a contributing factor in the deaths of a number of infants whose deaths have been ascribed to other specific causes. For example, when a cause for premature delivery could be found, such as placenta previa, the cause of the fetal death was ascribed to the placenta previa. Similarly, when the premature infant had a congenital defect, the defect was listed as the cause of death.

The difference between the private rate and the ward rate is not statistically significant. The difference between the ward Negro rate (4.7 per thousand) and the ward white rate (3.4 per thousand) is not significant. However, when those infants born alive before the twenty-eighth week are included, the ward white rate becomes 6.4 per thousand and the ward Negro rate becomes 11.2 per thousand, a statistically significant difference.

It appears that prematurity is a constant cause of fetal death in about 7 cases per thousand births among white patients, both ward and private, and in about 11 cases per thousand births among Negro patients. It is noteworthy that no apparent change in these rates has occurred in ten years. Furthermore, there has been no statistically valid change in the salvage rate of premature infants during these years. This suggests that the rates are the result of natural forces present in the child when he is born (such as degree of development of the lungs) over which no control can be exercised at present. But the difference in the Negro patients, whose living and health standards are inferior to those of the white patients, suggests that even these physical factors can be influenced by improving the general condition of the mother.

It is also noteworthy that the number of infants born alive before the twenty-eighth week is increasing. These infants still have a high mortality rate, and hence improvement in the mortality rate for prematures over 28 weeks will be balanced out by deaths among the group born alive before 28 weeks.

During the period of this study the management of labor in the presence of prematurity has been most carefully planned. Sedation has been limited with close attention being paid to oxygen supply to mother and child, and with adequate episiotomy done under conduction anesthesia. In 223 cases of

vertex delivery in which autopsy was performed 212 (or 95 per cent) were delivered spontaneously and 11 by forceps. Intracranial hemorrhages of small extent were found in 16.6 per cent of those delivered spontaneously and in 57 per cent (6 of the 11 cases) of those delivered by forceps.

Pediatric care has also been most detailed in the nurseries and in the Babies Hospital. Further improvement in the mortality from prematurity will depend on new advances in the management of these infants, but from the obstetrical point of view improvement will come from an understanding of the causes of premature labor and its prevention. It is of interest in this latter respect to note in the mothers of these infants the conditions associated with prematurity to which a causative influence might be attributed. These conditions are shown in Table IV.

TABLE IV. CONDITIONS ASSOCIATED WITH PREMATURITY (INCLUDING LIVE BIRTHS UNDER 28 WEEKS)

	WARD		PRIVATE		TOTAL	
	CASES	PER CENT	CASES	PER CENT	CASES	PER CENT
1. None	99	29.4	73	40.7	172	30.0
2. Toxemia of pregnancy	63	18.7	15	8.4	78	15.1
3. Twins	34	10.0	9	5.0	43	8.3
4. Congenital defect	32	9.5	16	9.0	48	9.3
5. Premature separation of placenta	30	8.9	15	8.4	45	8.7
6. Premature rupture of membranes	24	7.1	16	9.0	40	7.7
7. Fetal disease	17	5.0	7	3.9	24	6.5
8. Placenta previa	12	3.6	11	6.1	23	6.3
9. Induced labor	10	3.0	9	5.0	19	3.6
10. "Placental insufficiency"	9	2.7	5	2.8	14	2.6
11. Rupture of uterus	3	0.9	2	1.1	5	0.9
12. Congenital malformation of uterus	2	0.6	1	0.6	3	0.6
13. Mother died undelivered	2	0.6	0	0	2	0.4
Totals	337	100.0	179	100.0	516	100.0

It is seen in Table IV that about 30 per cent of these cases had no demonstrable cause for the premature labor. This group deserves further study, but at present no means of preventing labor before term is known. In the remaining cases a division according to theoretical preventability can be made. At present, theoretical control can be exercised over those cases with toxemia, and those in which delivery was induced before term, a total of 97 cases (19 per cent). The remainder are not preventable in the present state of our knowledge.

6. Birth Trauma.—These are cases in which death is demonstrated by autopsy to be due to specific pathological lesions produced by trauma, of which laceration of the tentorium is the most frequent example. These cases are very clear-cut. The difference between the ward and private rates is statistically significant.

The type of delivery associated with fetal death from birth trauma is shown in Table V. These represent a total of 85 cases, 65 on the ward service and 20 on the private service. Theoretically, all of these would have been saved by cesarean section, but practically it is not always possible to select these cases. However, it was possible to gain a very strong impression that all the information necessary to indicate cesarean section was already at hand in certain cases at the time that the vaginal procedure listed in Table V was chosen. If these cases are selected, it is found that 42 of 65 ward cases (65 per cent) and 12 of 20 private cases (60 per cent) should have been treated by cesarean section. The acceptance of this point of view is shown by an increasing incidence of cesarean section during these years, and a decreasing incidence of traumatic deliveries from below.

TABLE V. DEATHS FROM BIRTH TRAUMA ACCORDING TO TYPE OF DELIVERY

	VERTEX				BREECH			VERSION AND BREECH EXTRACTION
	SPONTANEOUS	LOW FORCEPS	MID-FORCEPS	HIGH FORCEPS	SPONTANEOUS	ASSISTED	EXTRACTION	
Ward	11	3	15	3	1	6	12	14
Private	4	3	4	0	0	0	3	6
Total	15	6	19	3	1	6	15	20

7. Fetal and Neonatal Diseases.—In this category are grouped those cases in which the cause of death was dependent entirely on fetal factors. It includes cases of fetal death in utero due to erythroblastosis and to congenital pneumonia as well as neonatal deaths. This grouping is made on the basis of the autopsy findings. The difference between the two services is statistically significant. The pathological diagnoses in the cases of fetal and neonatal diseases are shown in Table VI.

TABLE VI. AUTOPSY FINDINGS IN CASES OF FETAL AND NEONATAL DISEASE, GROUPED ACCORDING TO THEORETICAL PREVENTABILITY

DISEASES	STILLBIRTHS		NEONATAL DEATHS	
	WARD	PRIVATE	WARD	PRIVATE
Nonpreventable.—				
Erythroblastosis	13	4	9	3
Hemolytic disease (non Rh)	0	0	1	1
Major group incompatibility	1	0	0	0
Hyaline membrane	0	0	3	2
Thrombosis of cerebral vessels	0	0	1	0
Toxoplasmosis	1	0	1	0
Volvulus	0	0	1	0
Cystic fibrosis of pancreas	1	0	0	0
Diffuse necrosis of liver	0	0	0	2
Rupture of stomach, cause unknown	0	0	1	0
Total nonpreventable	16	4	17	8
Preventable: Infections.—				
Congenital pneumonia	4	0	4	0
Lobar pneumonia	0	0	1	0
Staph. parotitis	0	0	1	0
Acute esophagitis	0	0	2	0
B. coli meningitis	0	0	0	1
Total	4	0	8	1
Preventable: Noninfections.—				
Congenital atelectasis	0	0	0	1
Asphyxia and myocardial necrosis	0	0	2	0
Aspiration pneumonia	0	0	4	0
Total	0	0	6	1
Total preventable	4	0	14	2

Nonpreventable diseases: The first category contains those cases for which no prophylactic measures can be taken at present, a total of 33 ward and 12 private cases. Two-thirds of these are due to erythroblastosis. The apparent difference between the ward and private services is not significant statistically.

Preventable diseases: Only two (of 13) deaths in the infectious group have occurred in the past five years. Both of these patients had a long period of ruptured membranes but did not receive prophylactic antibiotics, and both babies died of congenital pneumonia. This group seems to be potentially entirely preventable with antibiotics. At the Sloane Hospital for Women all ward patients with ruptured membranes are admitted to the hospital for prophylactic antibiotic treatment. This usually consists of 800,000 units of

Crysticillin per day. If the patient is sensitive to penicillin another antibiotic is chosen. The treatment is continued until the leakage ceases or the patient is delivered. Private patients are treated in the same manner in most cases. Occasionally, when the rupture occurs early in the third trimester, the treatment is carried out at home.

In the noninfectious group there are 7 cases, and here improved obstetrical handling might have prevented death. In the one case of congenital atelectasis and in the two cases of asphyxia with myocardial necrosis the mothers were sedated heavily shortly before delivery. This may have been a factor in the deaths of these infants. Two patients with aspiration pneumonia delivered unattended.

The fetal and neonatal disease categories consist then of a total of 65 cases, of which 45 are not preventable at the present time. The 13 infectious cases are all preventable, and are now being prevented. The 7 noninfectious cases are all preventable with better obstetrical care.

8. Premature Separation of Placenta.—In this category are those cases in which there was clinical evidence of premature separation of the placenta. These varied from cases presenting scant vaginal bleeding with clot adherent to the placenta to the characteristic syndrome of abruptio placentae. There were 19 cases before term, and 29 at term. Pre-eclampsia was present in 5 before term and 7 at term. The small difference between the ward and private services is not significant. The numbers per year are so small that no reason for this slight difference can be demonstrated.

9. Miscellaneous.—This is a small group of 14 cases (10 ward and 4 private) made up of isolated causes, for example, a patient who died undelivered at 30 weeks of lymphosarcoma, or one patient in whom spinal anesthesia was accompanied by a profound fall in blood pressure and asphyxia of the child. These are rare cases which follow no pattern, and are so few that statistical treatment is of no value. It is of interest that the number of these cases on the ward is greater than would be expected from the ratio of total numbers of patients on ward and private services.

10. Placenta Previa.—This is now an infrequent cause of fetal death, there being 9 cases on the ward service and 5 on the private service. Some of these infants died before birth, but the majority died after delivery, of prematurity and/or the effects of asphyxia. When the cause of the prematurity was placenta previa, and the child died of prematurity, the death was listed under placenta previa. Since the total number of cases in the ten years was 14, statistical treatment of the data is of no value, but it is of interest that the number of cases on the ward service is greater than would be expected from the ratio of the numbers of ward and private patients.

Comment

The data presented above show that the stillbirth and neonatal mortality rates at the Sloane Hospital for Women have decreased slightly during the decade 1940 to 1949, but the decrease is not statistically significant. This is due to the fact that the rates at the beginning of the decade were already low, and the amount of improvement possible was not great. However, the rates for the private service have been consistently and significantly lower than those for the ward service. Maximum improvement should yield similar rates for both services, when any so-called irreducible minimum is reached.

By examination of the various causes for fetal and neonatal mortality, the difference between the two services is seen to exist in *every category*. This difference is statistically significant in four categories: maternal disease, cord complications, birth trauma, and fetal and neonatal diseases. The dif-

ference in the rates due to congenital defect is on the border line of statistical significance. The difference is not statistically significant in five categories: prematurity, unknown, premature separation of placenta, miscellaneous, and placenta previa, although in each instance the difference is in favor of the private service.

There are two reasons for the differences between the two services: (1) an increased incidence of the conditions causing death on the ward service, and (2) better obstetrical care on the private service. It is demonstrated above that the difference in the categories of maternal diseases, congenital defect, and fetal and neonatal diseases is due solely to an increased incidence on the ward service. This may be explained for maternal and fetal and neonatal diseases partly by the better state of health of the private patients due to their more favorable economic and social circumstances. But superior quality of obstetrical care also reduces these diseases, and for this reason the relative importance of economic status and obstetrical care cannot be gauged in this study. Congenital defects, on the other hand, offer only a field for speculation. The data do not indicate the cause of this difference. The suggestion is offered that certain of these cases may be due to maternal disease rather than to "poor germ plasm" alone, and that the same factors of economics and better obstetrical care operating in the general category of maternal diseases also operate here.

In the categories of cord complications and birth trauma it is obvious that the difference lies in better obstetrical care on the private service. The incidence of cord complications is the same on the two services, but more children are saved on the private service. Birth trauma is more successfully avoided on the private service.

In the three categories of premature separation of the placenta, miscellaneous, and placenta previa, the differences are probably not significant (in a statistical sense), and yet the same two factors of economic status and quality of obstetrical care can be seen operating in these groups as well.

It is also desirable to determine, if possible, what measures might be taken to diminish the fetal and neonatal mortality whether on ward or private service. For this purpose, the cases have been divided into three groups, those probably preventable, those possibly preventable and those not preventable. By this division, those now "probably preventable" (28 per cent) comprise all of the maternal disease group, all of the birth trauma group, and 30 per cent of the fetal disease group, a total of 239 ward and private cases. Those "possibly preventable" (33 per cent) comprise the groups of cord complications, premature separation of the placenta, placenta previa, and prematurity, a total of 281 cases. The remainder (39 per cent)—unknown, congenital defects, miscellaneous, and 70 per cent of the cases of fetal disease—are not preventable.

Ideal obstetrics, in the light of present knowledge, would prevent 61 per cent of the fetal and neonatal deaths in this study. It is obviously impossible, on a practical basis, to achieve this goal, but such a calculation presents a hypothetical ideal toward which progress can be made. This goal is represented by a fetal mortality rate of 13.0 per thousand (stillbirth rate 6.7; neonatal mortality rate 6.3) on the ward, and 8.7 per thousand (stillbirth rate 4.6; neonatal mortality rate 4.1) on the private service. The difference between the two services persists even in this calculation, and is an expression of lack of knowledge concerning the causes of death represented in the nonpreventable group. Such knowledge will appear in time, so that the figures calculated above represent a *minimum* which is *irreducible* only in the light of present knowledge.

Summary

1. The fetal mortality on the ward and private services at the Sloane Hospital for Women for the years 1940 to 1949 has been reviewed.

2. There has been a slight decrease in fetal mortality on both services during this decade, but the decrease is not statistically significant.

3. There is a statistically significant difference between the fetal mortality rates on the ward and private services. This difference appears to be due to the better health of the private patients, and better obstetrical care on the private service.

4. The causes of fetal mortality have been listed *according to the obstetrical point of view,* and the possibility of improving the results under each cause has been discussed.

5. A division has been made into degrees of preventability *within the limits of our present knowledge.* It appears that 28 per cent are probably preventable, 33 per cent are possibly preventable, and 39 per cent are not preventable. Ideal obstetrics, as understood at present, would thus produce a fetal mortality of 13.0 per thousand on the ward service and 8.7 per thousand on the private service. This difference in the "ideal" figures (ideal at present) between the ward and private services expresses a lack of knowledge concerning certain causes of death which cannot be filled in at present.

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A CRITICAL STUDY OF ECLAMPSIA IN A MUNICIPAL HOSPITAL*

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THE great progress of the past two decades in the treatment of the complications of pregnancy has served to emphasize through contrast the lesser advance in the treatment of eclampsia. To be sure, the importance of antepartum care directed toward the prevention of pre-eclampsia and eclampsia has greatly lowered the incidence of severe cases in those parts of the country where adequate care by modern standards is available, and the improved results are largely due to early recognition of symptoms manifested by rapid weight gain, and constitute a gratifying result of preventive effort. However, once the eclamptic seizure has occurred in the antepartum or intrapartum period, the prognosis becomes much less favorable for both mother and infant.

In a large city, eclampsia is becoming a rare condition and the opportunity to review the treatment of a significant number of cases does not commonly present itself. Critical evaluation of successes and failures and modification of treatment depends on clinical trial. Too often a mode of therapy becomes stagnant when only two or three cases a year are admitted, and re-examination is required for evaluation. It was for the purpose of appraising the results for mother and infant in the hands of the resident staff, under supervision of the visiting staff, in a municipal hospital that this study was undertaken. The treatment of eclampsia at Fordham Hospital is believed essentially similar to that in use in most hospitals in the United States, and, despite the small number of cases, this series is considered worthy of critical examination.

Material

During the period from January, 1940, to December, 1950, there were 27 patients hospitalized on the obstetrical service with the diagnosis of eclampsia. The diagnosis was made on the basis of the classic signs of toxemia plus convulsions. All the patients had one or more convulsive seizures. There were two maternal deaths in the series, a mortality rate of 7.8 per cent. There were 14 fetal and neonatal deaths in 26 of these cases, a fetal mortality of 55 per cent.

The total number of deliveries at Fordham Hospital during this period was 11,057. The incidence of eclampsia is 0.24 per cent for this eleven-year period. This is about one-third the mean incidence of eclampsia in the United States, given as 0.66 per cent.[1] The true incidence in the population using this municipal hospital is even lower because twelve of these patients were from the private practice of local physicians, and were referred because of the complication, having been scheduled for delivery elsewhere. Nine patients admitted to no antepartum care prior to admission, and six were patients who had been seen in the clinic. This group of 15 patients may be regarded as representing the true incidence in the population using this municipal hospital.

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There is no way of knowing what proportion of patients in the district are delivered by private physicians and no statistical inference can be attached to the high proportion of eclamptic patients from that source. In general, however, about 85 per cent of patients delivered in this hospital are first seen in the clinic, and about 15 per cent admit to no care. It is statistically significant that this 15 per cent contributed 60 per cent of the cases of eclampsia other than those referred by private practitioners.

The average age of the patients was 30 years, and they ranged in age from 16 to 44. The distribution of half the patients fell between 21 and 30 years.

This series comprises 16 primiparas and 11 multiparas. Of the multiparas, two were gravida ii, three were gravida iii, one was gravida iv, two were gravida v, and three were gravida vi. This varies a little from the usually accepted ratio of primipara to multipara of 3:1.[1]

Eighteen patients had convulsions in the antepartum period, ranging from the twenty-sixth week to the thirty-ninth week, at an average of 32.6 weeks. Of this group of antepartum eclamptic patients, 14 were primiparas and 4 were multiparas. In the multiparas there was no relationship between parity and the time of convulsion in the pregnancy. There was one intrapartum convulsion in a term pregnancy in a primipara.

Eight patients had postpartum convulsions. Seven of these were multiparas, and one a primipara. These occurred from one to sixteen hours post partum at an average time of onset of just under six hours. This is a striking incidence in relation to parity, inasmuch as 87.5 per cent of postpartum seizures were contributed by 40 per cent of the patients; however no statistical evaluation may be drawn from a small series with any confidence.

As to premonitory symptoms, there were twelve mentioned. Four patients denied any symptoms at all. Thirteen mentioned headaches, fourteen edema, nine vomiting, four visual blurring, three epigastric pain, two each heartburn, nausea, insomnia, and one each oliguria, backache, diarrhea, and chills. Two gave histories of high blood pressure, three of prior eclampsia, and one of nephritis.

On admission to the hospital fifteen patients were comatose, seven described as not comatose, and five as irrational.

An attempt was made to separate the cases of toxemia of pregnancy unheralded by prior history from those cases with underlying hypertension, nephritis, or prior toxemia with hypertensive sequelae upon which toxemia with eclampsia was superimposed. Aside from history and eyeground changes suggestive of chronic hypertensive states, there was no way in which this could be accomplished, in those with no care. No attempt was made to establish the patient's status in this respect at the time of the antepartum examination prior to the twenty-fourth week of pregnancy in those referred by private physicians. This was in order to assess the importance of a pre-existing hypertension on the course of the pregnancies in this series which terminated in eclampsia, and see if the fetal mortality in this group was significant.

As there are conflicting reports in the literature as to the influence of pre-existing hypertension on maternal and fetal mortality[2, 3, 4, 5] in eclampsia, it is perhaps of prognostic and therapeutic importance to weigh the factors contributory to any given case of toxemia and eclampsia. Chesley and Annito[3] reviewed 301 pregnancies in 218 women with hypertensive disease known to have existed before pregnancy, using a standard of 140/90 or greater. The gross fetal loss, with and without prior toxemia in 840 prior pregnancies for this group was 34.8 per cent, in the first hypertensive pregnancy observed, 38 per cent, and in subsequent pregnancies the gross fetal loss was 40 per cent.

The fetal loss increased with the higher initial pressure, second trimester rises in blood pressure, and the higher the blood pressure near delivery. Torpin and Bryans,[2] on the other hand, found in a series of 106 pregnancies in 34 hypertensive women a gross fetal loss of 17 per cent, only slightly higher than the incidence of stillbirths of 2.14 per cent and abortions of 8 to 10 per cent reported by Stander.[6] This is in agreement with the series reported in 1946 by Sharkey and Hess[4] who found infant mortality, abortions, and premature deliveries no more frequent in 115 hypertensives than in normal patients. Of hypertensive patients, two-thirds may be expected to escape toxemia, and in the series reported from the Margaret Hague Hospital, the fetal loss in this group was 18.5 per cent. Among the one-third that developed toxemia, there was a total maternal mortality of 12.2 per cent, ten times that in the group of uncomplicated cases, and a fetal mortality of 50 per cent, three times that in the group with uncomplicated hypertension. Irving[7] reported a total fetal mortality of 45 per cent in eclampsia and pre-eclampsia in a series of 33 infants, and Wilson[8] a total fetal mortality of 37.3 per cent in 66 cases of eclampsia. DeLee and Greenhill[9] state that the average fetal mortality in the United States is 40 per cent in eclampsia.

There were eight patients in our series whose toxemia was considered to be on a basis of prior hypertension. These were of the average age of 33 years. There were 19 cases which were regarded primarily as toxemia with no antecedent hypertension, and these patients averaged 28 years of age. This relationship to age is to be expected.

Since in one of these cases delivery had been at home, the fate of the baby could not be ascertained. Of the remaining seven infants, three were stillborn, all the mothers having had antepartum convulsions between the twenty-eighth and thirty-second weeks, and four were born living and survived, the mothers in all these last cases having had postpartum convulsions. The fetal mortality of 42 per cent in the cases of hypertension is similar to that in the entire series.

However, this category, namely, toxemia superimposed on a pre-existing hypertension, included both the maternal deaths in the series. One of these patients was 39 years of age, and the other 41, significantly above the average of 30 years for the series, and in keeping with the figures compiled by Chesley and Annito with respect to increased maternal risk in toxemia in hypertensive disease.

Three of our patients gave histories of eclampsia with prior pregnancies. The first was a 35-year-old gravida v, para i, who had chronic kidney disease, and had had convulsive seizures with two prior pregnancies. During the confinement represented in this series she had one postpartum convulsion. Her eyegrounds showed characteristic hypertensive retinitis. The fate of the baby is not known. A second patient was a 41-year-old gravida iii, para i, who, four years before, had had eight convulsions with the delivery of a stillborn infant at another hospital. Two years later she had had a normal delivery after strict supervision. She was delivered of a stillborn infant by cesarean section, having improved after having two convulsions at 34 weeks' gestation. The third patient was a 31-year-old gravida vi, para v, first seen in 1943 when she had three convulsions four and five hours post partum despite prophylactic morphine injection two hours before the first seizure. One year later she had a second episode of eclampsia manifested by a single convulsion 11 hours post partum, again despite morphine. During hospitalization the eye consultant described marked arterial narrowing with an arteriovenous ratio of 1:4, and exudates, a picture typical of malignant nephrosclerosis. It is of interest that this last patient twice delivered living and surviving babies, having twice signed herself out on her own responsibility and against advice in severe pre-eclampsia. Her second pregnancy went to term despite a blood pressure of 184/120 as early as the twentieth week, and albuminuria commencing about the thirtieth week.

While many of the symptoms and complications of toxemia are thought to be due to hypertension, it is difficult to correlate these with the degree of hypertension. There was no correlation between the level of hypertension and the number of convulsions. In 17 of 27 cases the diastolic pressure was above 110 mm. Hg, and in 15 the ratio of systolic to diastolic was under 1.7, the average of these being 1.53. Recent reports have emphasized the increase of diastolic pressure as being a particularly bad prognostic sign, using as an index the systolic: diastolic ratio.[11] The ratio in essential hypertension patients has been determined to be 1.7. Complications are likely in toxemia if the ratio falls below 1.5.

As to the occurrence of albuminuria in eclampsia, three and four plus was the rule, but in three cases in the series, the urine was persistently negative for albumin.

Of the twenty cases in wihch the urinary output was measured, it fell below 1,000 c.c. in the 24 hours following the eclamptic seizure in 17 cases. The average urinary output in the first 24 hours was 575 c.c. for these 20 patients, ranging from a minimum of 50 c.c. to a maximum of 1,425 c.c. The average output in the second 24 hours was 685 c.c. No patients were anuric.

Blood urea nitrogen levels were slightly elevated in the large majority of patients, being between 25 and 35 mg. per 100 c.c. There were three cases with urea nitrogen levels above 40 mg. per 100 c.c., one of which ended fatally with a level of 100 mg. per 100 c.c. terminally. Blood uric acid levels ranged from 3.8 mg. per 100 c.c. to 7.8 mg. per 100 c.c. and averaged 5.5 mg. per 100 c.c.

Despite the grading of two-thirds of the antepartum cases as severe eclampsia, there was no significant premature separation of the placenta in this series. The criteria used to classify the cases in this series are those used at the Chicago Lying-in Hospital.[9]

TABLE I. CLASSIFICATION AND GRADING

CLASS	NO.	PER CENT	MILD	PER CENT	SEVERE	PER CENT
Ante partum	18	66.6	6	33	12	66
Intra partum	1	3.9	1	100		
Post partum	8	29.5	4	50	4	50

There was a total of 86 convulsive seizures in 27 patients, for an average of 3.35 seizures per patient. They ranged in number from 1 to 15 in individual cases. The number of seizures bore no relation to parity, to occurrence antepartum or postpartum, or, as noted, to the level of the blood pressure. The number varied from 1 to 10 in the convulsions which occurred ante partum, and from 1 to 15 in those occurring post partum. The time relation varied over a wide range from three seizures in 72 hours to 15 in 13 hours. In two cases convulsions recurred 9 and 18 days, respectively, after a series of convulsions had apparently responded to treatment, and while the patient was in the hospital.

In controlling the convulsions, morphine was the drug most commonly used, usually in ¼ grain doses, occasionally in ½ grain doses. Magnesium sulfate, phenobarbital, Sodium Amytal, sodium bromide, chloral hydrate, Demerol, paraldehyde, ether, Pantopon, and scopolamine were also used in about that order of descending frequency. Intravenous 50 per cent dextrose was routinely employed.

Of 27 cases, 13 were successfully treated in that there was no recurrence of convulsions after treatment was started. Fourteen cases must be regarded as therapeutic failures if we are to accept this criterion of the success of

immediate therapy in eclampsia, in that among these 14 there was an average of 2.3 convulsions per patient after entering the hospital, and after treatment had begun.

One patient weighted this series to a disproportionate degree in that she had 12 seizures after treatment started. She was a 33-year-old gravida vi, para vi, admitted to the hospital in 1943, eight hours postpartum, with a history of a convulsion at home, in convulsion on admission, with all the classic signs of a full-blown eclampsia. She received ¼ grain of morphine four times, ⅙ grain once, ⅓ grain of Pantopon once, and, in addition, bromide, chloral hydrate, phenobarbital, and magnesium sulfate in the course of thirteen hours. This eclampsia could not be controlled by the dosages of morphine and other hypnotics used. A 29-year-old primagravida in this series entered the hospital in convulsion in her twenty-sixth week of pregnancy and received 300 mg. of Demerol, and 26 grains of parenteral Sodium Amytal in addition to phenobarbital and magnesium sulfate in the first twelve hours. Respirations were markedly depressed, and, because of the combination of drugs used, it was difficult to determine and maintain an effective level of sedation. Another patient who presented this difficulty received morphine, Sodium Amytal, Demerol, magnesium sulfate, and paraldehyde in fourteen hours.

When such an assortment of drugs is used that the control of the depth of sedation is difficult, deeper sedation than is necessary may result, with added jeopardy to the baby. The high fetal death rate in eclampsia may be in part attributable to therapy as well as to the convulsions, toxemia, and prematurity. As stated by Cosgrove and Chesley,[12] "Every sedative available in eclampsia is a poison, and to multiply the number of such agents simultaneously given to a patient is to risk the incalculable synergistic effect of several poisons on a woman already manifestly severely poisoned."

TABLE II. RESPONSE OF CONVULSIONS TO TREATMENT

NO. CONVULSIONS AFTER THERAPY	NO. OF PATIENTS WITH CONVULSIONS		
	ANTE PARTUM	INTRA PARTUM	POST PARTUM
0	10*		4
1	4	1	
2	2		1
3	1		2
4-5	1		
6-10			
10-15			1

*A second seizure occurred in 9 days.

It is of interest that our experience in this respect was paralleled at the Rotunda in Dublin during therapy of the first thirteen of a series of 33 eclamptics with morphine, magnesium sulfate, and hypertonic glucose.[13] An average convulsion recurrence rate of slightly under three seizures per patient after therapy was commenced was experienced. Treatment with a 0.3 per cent Pentothal drip in 10 per cent dextrose solution in water gave superior results. Avertin in 3 per cent solution for rectal instillation as reported by Dewar and Morris[14] and continuous spinal anesthesia as reported by McElrath and associates[15] have both resulted in more effective control of the seizures. It was our impression that Sodium Amytal, used both intravenously and intramuscularly, was at least as effective an anticonvulsant as morphine, but we have had difficulties in controlling the dosage.

From Table III it will be seen that almost 90 per cent of the recurring seizures occurred more than two hours after the onset of therapy. This can mean only that effective sedation was achieved at the outset, but that as the

drugs were either destroyed or excreted the level of sedation fluctuated sufficiently to lower the threshold for convulsion. It would appear that one of the important criteria for treatment in eclampsia is the maintenance of a nonfluctuating level of sedation, and, in this respect, the continuous administration of a short-acting drug would seem most promising.

TABLE III. TIME REQUIRED TO CONTROL CONVULSIONS

TIME	NO. OF PATIENTS WITH CONVULSIONS		
	ANTE PARTUM	INTRA PARTUM	POST PARTUM
Immediate	10*		4
30 minutes	1		
1 hour			
2 hours	1		
4 hours	3		1
7 hours			2
Above 8 hours	3	1	1

*A second seizure occurred in 9 days in one case.

Of the 27 cases of eclampsia in this series, the fate of the pregnancy is known in all but one case, a patient with postpartum convulsions who delivered at home and could not be traced. Of seven patients who convulsed post partum, one delivered a stillborn infant of 28 weeks' gestation, and the others delivered five babies and one set of twins, all of whom survived.

The eighteen patients with antepartum convulsions had eleven stillbirths at an average duration of pregnancy of 33 weeks, five living babies at an average duration of pregnancy of 35 weeks, and two neonatal deaths at an average duration of pregnancy of 30 weeks. The one patient with intrapartum eclampsia delivered a surviving baby.

The average number of convulsions experienced by the 13 patients who had eleven stillbirths and two neonatal deaths was 2.8. The average number of convulsions experienced by those patients with antepartum eclampsia who delivered surviving babies was 3.0. There was no significant relationship between the number of convulsions and the outcome of the pregnancy nor was there any significant relationship between the level of the blood pressure and the outcome of the pregnancy in this series.

There were five women who delivered stillborn infants who were eight months or more pregnant prior to the first convulsion. The fetal heart was audible in these patients on admission, and disappeared eight days, five days, four days, and two days (two cases) after the convulsions ceased. The average time was four days. Four of these patients were primagravidas, and all had improved after treatment.

There were five women who delivered living babies after antepartum convulsions. The time elapsed from convulsion to delivery in these cases was one, seven, twenty-two, twenty-three, and thirty days.

It would then appear that there is a certain critical period in those babies that survive the convulsion per se with the attendant anoxia, which in our series lasted an average of four days. If the toxemia was brought promptly under control and the patient was in condition to tolerate induction of labor within this period without aggravation of the toxemia, a better fetal salvage might result. McElrath's[15] series in which the elapsed time from onset of treatment to delivery was only 33 hours on the average for twelve cases with a 25 per cent fetal mortality is corroborative.

It seems proper to compute the statistics of fetal mortality on the basis only of those patients who had convulsions ante partum or intra partum. On this basis there were six surviving babies in 19 deliveries for a fetal mortality

of close to 70 per cent. This compares with a 65.6 per cent mortality in antepartum and intrapartum eclampsia reported by Tillman[16] in a series of 70 cases. Of seven known postpartum eclamptic patients, six had surviving babies, and if these figures are incorporated in the results, the fetal mortality falls to 55 per cent, above the average in recent series which is between 30 and 45 per cent. Statistics for fetal mortality are not comparable unless the weighting of series with antepartum and postpartum eclamptic patients is considered.

There were two maternal mortalities in this series:

CASE 1.—H. M., a 41-year-old white gravida iii, para i, was admitted Jan. 16, 1949, 34 weeks gravid, and in convulsions with a blood pressure of 200/120, 4+ albumin, and edema. She had one subsequent convulsion one-half hour later. A history was elicited of eight seizures and stillbirth at another hospital in 1945, and normal delivery two years before after a strict regimen. She responded to treatment and insisted upon going home. This was deemed inadvisable, and on Jan. 20, 1949, under 150 mg. of procaine spinal anesthesia and 3 minims of Adrenalin, a low-flap cesarean section was done. The blood pressure fell to 120/70 and ¾ grain of ephedrine was given intramuscularly. The baby was stillborn although the fetal heart was heard just prior to surgery. On the fifth postoperative day, after a relatively uneventful convalescence, the patient who was ambulatory had an episode typical of pulmonary embolism while at stool and died in a few minutes.

CASE 2.—E. F., a 38-year-old white gravida i was admitted Jan. 11, 1949, 28 weeks gravid, with a blood pressure of 225/120, 4+ albuminuria, and 4+ edema. Blood urea nitrogen was 13 mg. per 100 c.c. She had been under the private care of a general practitioner, and had fallen in a local theater just prior to admission. The fetal heartbeat was heard up to Jan. 19, 1949, when it disappeared concomitant with the development of pneumonia. The patient continued in a semicomatose state and on Jan. 23, 1949, she went into spontaneous labor and delivered a macerated stillborn infant. Following delivery she had a generalized convulsion which persisted in spite of intense sedation, and was terminated only on administration of open drop ether. She failed to regain consciousness, and the blood urea nitrogen gradually rose to 100 mg. per 100 c.c. She died on January 31, eight days post partum. The kidneys at autopsy showed cortical anemia with absence of red cells from the glomerular capillaries, the endothelium of which was thickened and agglutinated. Tubules showed cloudy swelling. The liver and spleen showed passive congestion. A confluent lobular pneumonia was present. The brain showed focal areas of edema and degeneration.

Other noteworthy complications in the series were a transient right hemiplegia occurring five days after a last convulsion, spontaneously subsiding in about 48 hours, and one transient paralysis of extraocular muscles affecting two or more muscles over a period of a week, subsequently disappearing completely.

Conclusions

A series of 27 cases of eclampsia has been reviewed.

The gross fetal mortality was 55 per cent; the fetal mortality in antepartum eclampsia was 70 per cent, in postpartum eclampsia 14 per cent.

The maternal mortality was 7.8 per cent.

The use of morphine, barbiturates, glucose, and magnesium sulfate at intervals for the control of convulsions is not satisfactory.

There is no relationship in this series between the number of convulsions, the height of the blood pressure, and the fetal survival.

Increased fetal survival should result from the application of means adequately to control the toxemia and seizures and the maintenance of a constant nonfluctuating control, followed by early delivery.

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THE ENDOMETRIUM AND ITS VASCULATURE OVERLYING SUBMUCOUS FIBROIDS IN RELATION TO UTERINE BLEEDING*

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IT IS generally accepted that the nearer to the inner surface of the uterus fibroids are located, the more they tend to change the amount or duration of bleeding. However, submucous fibromyomas may be found during hysterosalpingographies among patients whose single complaint is sterility, or after hysterectomies performed for pain or some other reason without any menstrual disorders. Why does not abnormal hemorrhage occur in all cases of submucous fibroids? This question has not yet received any satisfactory answer. Our knowledge of endometrial histophysiology has progressed a great deal in the last decade, because of the work of Barthelmez[1, 2] Daron,[5] Markee,[12, 13] Okkels,[15, 16] Engle,[15] and others.[8, 9, 10, 20] With the help of new data, it appeared interesting and useful to study again the endometrial mucosa and its vascular pattern lying over submucous fibroids. As far as terminology is concerned, the names "fibroid" and "myoma" will be given to leiomyomas, fibromyomas as well as to fibromas of the uterus.

The morphology of the endometrium covering submucous fibroids has been the subject of many discussions.

In the old literature before 1904, reported by Frankl,[7] Theilhaber and Hollinger,[19] the endometrial mucosa lying above submucous fibroids was inconstantly and inconsistently described as atrophic, normal in thickness, or hypertrophic.

Theilhaber and Hollinger[19] attributed the pathological uterine bleeding to some defect of the myometrial contractions on the oozing vessels. As far as the mucosa overlying submucous fibroids was concerned, these authors considered the variations of endometrial morphology as possible physiological changes of the uterine mucosa during the woman's life.

Frankl[7] stated that the submucous fibroids were accompanied by glandular atrophy. Furthermore, the author laid stress on the existence of a very rich subepithelial vascular plexus, the easy rupture of which was supposed to occur during the premenstrual uterine congestion or during some myometrial contractions. He suggested that some pathological bleeding might be explained in this way. However, it was not understood by Frankl why abnormal hemorrhage did not occur in 24 per cent of cases of submucous fibroids.

On the other hand, Sampson[17] and Faulkner,[6] by vascular injection methods of the fibromyomatous uterus, showed that the mucosa above submucous fibroids was anemic. Faulkner described the endometrium as "normal or abnormal

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histologically'' and he agreed with Theilhaber's theory that ''the bleeding might be contributed by the poor contracting power of the uterus due to the presence of the tumor.''

Cotte, Martin, and Rochet[3, 4] described various and inconstant lesions of edema, endometritis, atrophy, or hyperplasia of the mucosa, with some arteritis probably of syphilitic origin. In conclusion, the authors attributed hemorrhage chiefly to some ovarian dysfunction.

Material and Methods

The material for this study (25 uteri) has been selected among specimens from hysterectomies over a period of several years. Blocks were cut from the endometrial surface of fibroids after fixation ''en bloc'' in Zenker's or in Bouin's solutions. The slides were stained according to Masson's trichrome method which permitted the differentiation of muscle from connective tissue. Other blocks were cut from the uterus, cervix, tubes, and ovaries of the same specimens and stained with hematoxylin-eosin.

It is important to specify the *criteria which were followed* to select this material in cases of menstrual disorders. In the cases reported it must be first pointed out that although complete blood counts were made, prothrombin times were not regularly performed. No abnormality in the bleeding time or clotting mechanism was observed during and after the operative procedures, however. Likewise no heart or liver diseases were found which might produce any passive congestion of the pelvic vessels. The latter showed no gross abnormality at the time of the laparotomies. Furthermore, the patients had not recently received any estrogens or drugs such as Dicumarol or salicylates. Therefore, the causes of bleeding appeared to be related to primary gynecological diseases.

Moreover, in cases selected for this study, fibroids were grossly the single abnormality. The specimens with adnexal masses or with any other cervical or uterine tumors were not included in this material. The latter was composed of myomatous uteri with submucous fibroids and normal-looking cervices, tubes, and ovaries. The submucous fibroids were accompanied in most cases by intramural or subserous ones, the gross characteristics and the pathological diagnosis of which were found to be similar in the cases of normal menstruation as well as in those of abnormal bleeding.

As far as the hormonal influence was concerned, it was not feasible to measure routinely the various hormone levels during the menstrual cycle. Moreover, Te Linde[18] recently showed that ''functional'' bleeding—from a uterus in which there is no neoplastic or inflammatory lesion—might occur with any histological type of endometrium. If we except some cases of definite glandular hyperplasia or ''Swiss-cheese endometrium'' (Novak[14]) and perhaps a few cases of ''irregular shedding'' of the endometrium (McKelvey[11]), no morphological evidence of the ''functional'' type of hemorrhage has been found.

Therefore, only cases were included in which a menstrual period was still recognizable every month. This symptom suggested a rather normal cyclic activity of the ovary and excluded at least some important functional diseases as well as eventual postabortive bleeding. The following types of bleeding were reported by the patients of this series: normal menstruation in 10 cases, menorrhagia or metrorrhagia with recognizable menstrual cycles in 15 cases. Any menstrual bleeding lasting 5 days or less and having not shown any recent change in length or in amount was considered as normal. When having become definitely profuse or lasting regularly more than 8 days, it was called menorrhagia.

It is known that the endometrial vasculature is composed of straight and coiled arterioles, capillaries, veins, lymphatics and arteriovenous anastomoses.

As far as it can be deduced from Markee's endometrial transplants in the eye of the Rhesus monkey, arterial constriction appears at the end of the progestational phase. Each time an arterial vessel relaxes for a few minutes, bleeding occurs by hemorrage or diapedesis through arterial and capillary walls. Hematomas are formed in the stroma and rupture out of the mucosa which is shed simultaneously. This endometrial desquamation opens the veins. A secondary arterial oozing is also possible as long as the basal part of the coiled artery is not completely contracted.

Microscopic Findings

Leiomyomas, fibromyomas, as well as fibromas were found lying under the endometrial mucosa, without any interposition of normal myometrium. All types of endometrium were present above these fibroids. In the light of our present knowledge about the histology and physiology of normal menstruation, the different types of mucosa and their vascular pattern lying above submucous fibroids might be correlated with the various types of bleeding.

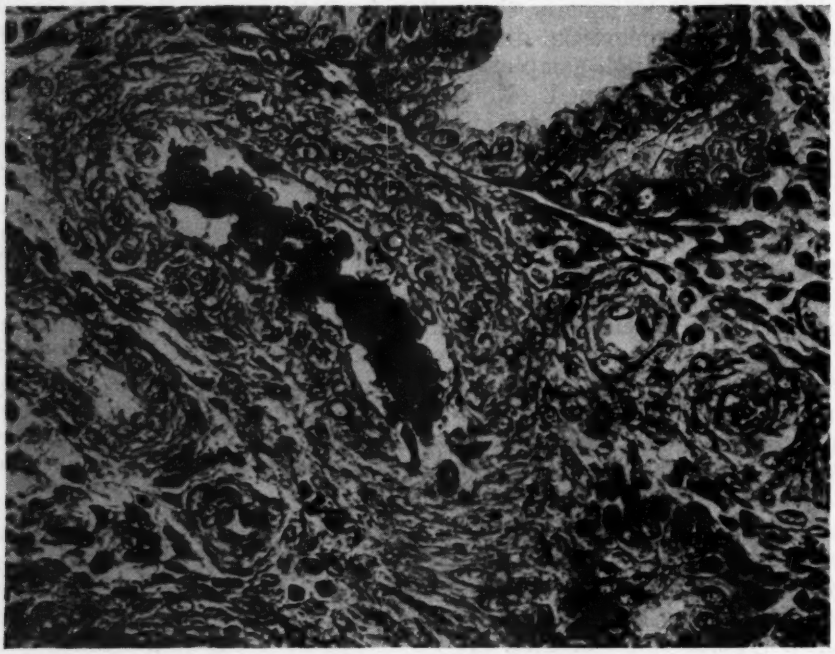


Fig. 1.—Glandular endometrium above submucous fibroid. Late secretory stage, normal coiled arteries. (×400.)

A. Glandular Mucosa.—

Mrs. H. C. (30393), 32-year-old Negro married woman, para 0, gravida i, noticed a painless but increasing enlargement of the lower abdomen of two years' duration. Her menstrual periods were always regular, lasting 4 days every 28 days. Her last menstrual bleeding was normal on Aug. 17, 1949. On Sept. 15, 1949, a complete abdominal hysterectomy with bilateral salpingo-oophorectomy was performed. The uterus weighed 1,130 grams and measured 20 by 13.5 by 12 cm. A large, firm fibroid, 14 cm. in diameter, occupied the fundus and the posterior wall and distorted the uterine cavity, which appeared hemorrhagic and velvety. Cervix and tubes appeared grossly normal, but microscopical chronic cervicitis and salpingitis were found.

The fibroid was sharply outlined from an endometrium with tortuous glands corresponding to the late secretory phase. The endometrial cells with ovoid basal nuclei had already

lost their apical secretions which still appeared as inspissated material in many glandular lumina. The stroma appeared slightly edematous with predecidual cells and moderate lymphocytic infiltration. Coiled arterioles (Fig. 1) were prominent and easily distinguished from the thin- and thick-walled venous vessels.

Fig. 2.

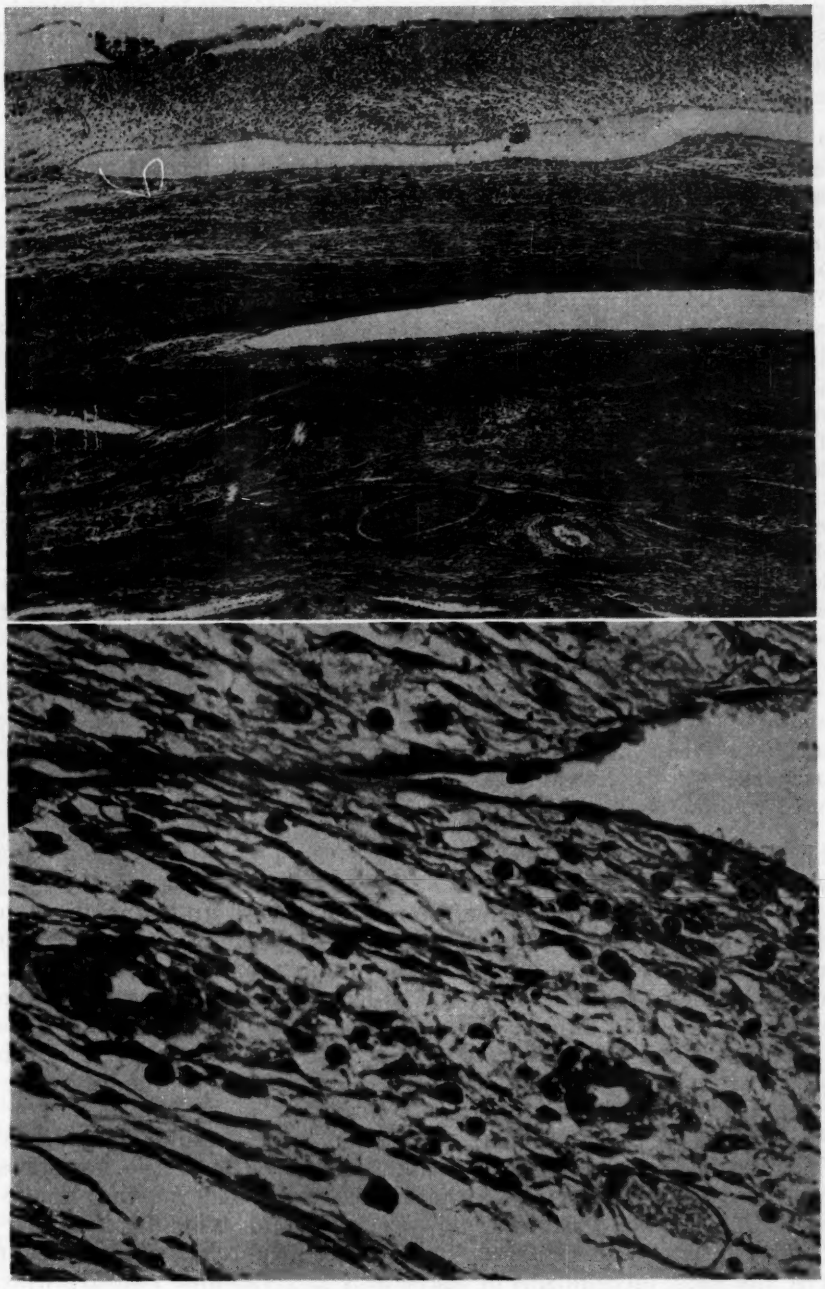


Fig. 3.

Fig. 2.—Congestive atrophic mucosa above submucous fibroid. Absence of glands, presence of large sinuses, ulcerated superficial epithelium. (×50.)

Fig. 3.—Congestive atrophic mucosa above submucous fibroid. Edematous stroma with large sinuses, degenerated arteries, and lymphoplasmocytic infiltration. (×400.)

This case represents a large, distorting, submucous fibroid covered by a normal mucosa with normal vasculature.

In the other cases with normal and regular menstruation not presented here in detail, glandular mucosa covered fibroids and showed glands at all the stages of the ovulatory and anovulatory cycles. Large veins might be seen in premenstrual endometria but in all the cases normal coiled and straight arterial vessels were present. Menstruation from the endometrium overlying these submucous fibroids was as normal as from an endometrium lying above normal myometrium.

B. Congestive Atrophic Endometrium.—

Various degrees of endometrial atrophy have been found above submucous fibroids by all investigators.

Mrs. E. A. (31620), 45-year-old white married woman, para i, gravida i, was quite well until 1948 when she began to have menorrhagia of 10 days' duration without any dysmenorrhea. Her last menstrual period began on Feb. 18, 1950. On March 2, 1950, a complete abdominal hysterectomy with right salpingo-oophorectomy was performed. The uterus weighed 670 grams and measured 13 by 9 by 10 cm. Several intramural and subserous fibroids, 1 to 8 cm. in diameter, were found. The uterine cavity was entirely occupied by a firm, irregular tumor, 3.5 cm. in diameter, with sessile base, arising from the anterior wall. The patulous cervix showed chronic cervicitis. No salpingitis was found in the tube.

The compact fibromyomatous tissue progressively blended into a very edematous stroma which did not contain any glands and was covered by the superficial epithelium, which showed a few mitoses. The cells became flattened at other places and there were even some denuded areas where a plasmolymphocytic reaction was present (Fig. 2).

The most striking feature of this highly edematous and nonglandular mucosa was the presence of some very long and broad sinuses lying parallel to the superficial epithelium. Blood cells were seen in the sinuses and in the surrounding stroma. No coiled artery was present. Only a few isolated arteries were seen in the lower part of the stroma. They showed the usual round lumina but their coats did not have the normal acidophilic muscle cells disposed in concentric layers around the endothelia. The latter were surrounded by hyalinized tissue which contained definite collagen fibers and some nuclei of variable size disposed around the vascular lumen. These nuclei might be very reduced in number and even be confused with the nuclei of adjacent fibroblasts (Fig. 3).

This description represents the usual features of an atrophic mucosa found at some place above a submucous fibroid. When the mucosa of the endometrial cavity was followed from the normal glandular mucosa up to the above-described atrophic endometrium, the stroma progressively became much more edematous than in the normal endometrium and the number of glands decreased. Veins and sinuses became prominent and the coiled arteries disappeared (Fig. 4).

Edema and dilated sinuses indicated some injury or mechanical occlusion of the lymphatic and venous circulation by the submucous fibroid. The blood flow appeared to be slower and this fact combined with the reduced arterial supply might explain the glandular atrophy.

As a matter of fact, vascular congestion, and presumably sluggish blood flow which normally occurs only during the last days of the menstrual cycle, is in these cases present during all the entire cycle. The increase in the uterine congestion during the premenstrual period would tend to increase further edema and dilation of the sinuses. Therefore, hemorrhage might occur in the stroma by the same mechanisms of diapedesis and vascular rupture which occur in any organ in chronic vascular congestion. This extravasated blood might build interstitial hematomas, which might rupture outside through the mucosa. Thus it is quite possible that menstruation starts earlier in this type of mucosa above submucous fibroids.

When menstruation does start, the flow appears to be longer. The shedding of the mucosa opens veins and sinuses. This venous type of hemorrhage contributes to the normal menstrual flow, and in these cases where the vascular congestion is much greater, it may persist and prolong the flow. However, the arterial defect appears to be another factor in protracted bleeding. It is known that in normal menstruation bleeding occurs in a part of the mucosa every time that the basal part of the coiled artery relaxes for a few minutes and that hemorrhage ceases when this artery contracts. In this case, the coiled arteries have disappeared and the rare arteries seen in the basalis of the endometrium do not have normal muscular tunics. Consequently the local hemostatic mechanism, which in Markee's endometrial transplants pervents the excess of bleeding from arterial hemorrhage or secondary arterial oozing, was found here to be strongly impaired. It may be said also that the delicate endometrial arteriovenous anastomoses are likely to be destroyed and this other eventual factor in the regulation of the endometrial blood flow is also lost.

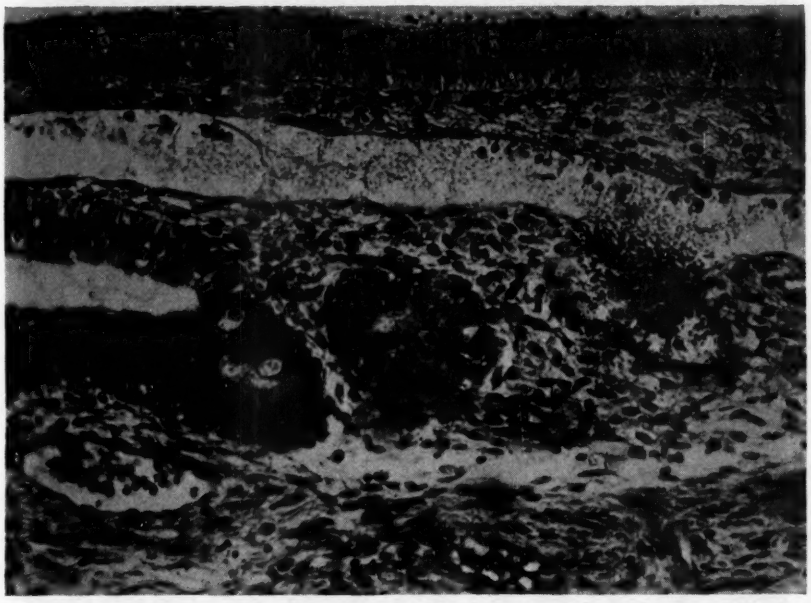


Fig. 4.—Congestive atrophic mucosa above submucous fibroid. Some glands are left, large sinuses are present. (×270.)

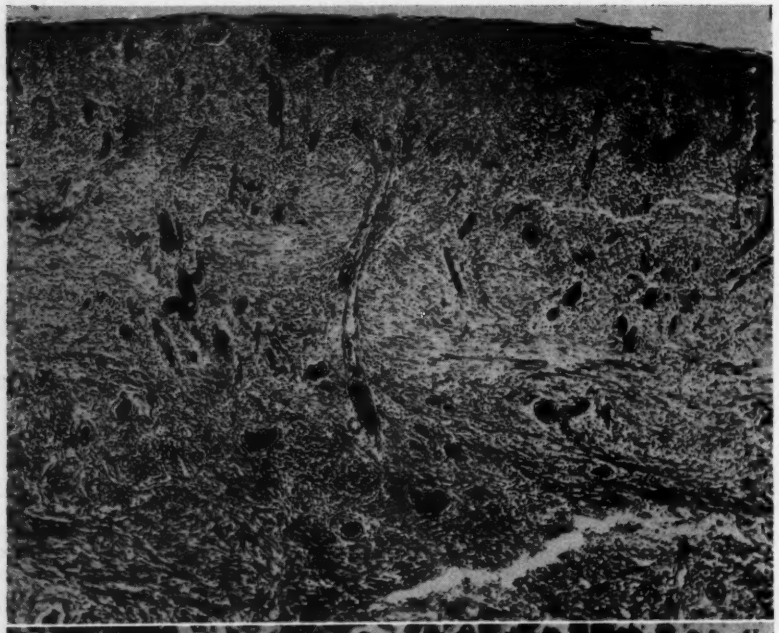
C. Ulcerated Fibroids.—

Mrs. A. J. (30742), 40-year-old Negro married woman, para 0, gravida 0, noticed a painful mass in the left lower quadrant four months before the operation. For the last two months, she had more profuse and painful menstrual periods than previously and she had been spotting intermittently between her periods. For two weeks a small mass, polyplike, had protruded from the vagina when she strained at stool. The last menstrual period began on Oct. 16, 1949. On November 3, a complete abdominal hysterectomy with left salpingo-oophorectomy was performed. The uterus weighed 500 grams and measured 9 by 15 by 9 cm. It showed several intramural and subserous fibroids. The endometrial cavity was distorted by several tumor masses. The largest one measured 7 cm. by 4 cm. Its free end was hemorrhagic and slightly friable and projected through the cervix which microscopically showed some chronic cervicitis.

The pedunculate submucous fibroid was a highly vascularized ulcerated fibromyoma (Fig. 5). Glands and superficial epithelium had entirely disappeared and were replaced by bleeding collagenous tissue in which many veins and sclerosed arterial vessels were present.

All these vessels showed nothing but connective tissue walls and no muscle fibers. However, the arterial vessels showed round lumina surrounded by transversely disposed nuclei, while the veins were more elongated with thinner walls and longitudinally disposed nuclei (Fig. 6). No vessel appeared to be ruptured at this time of midcycle but there was much extravasated blood. Plasmocytes were also present in the bleeding area.

Fig. 5.



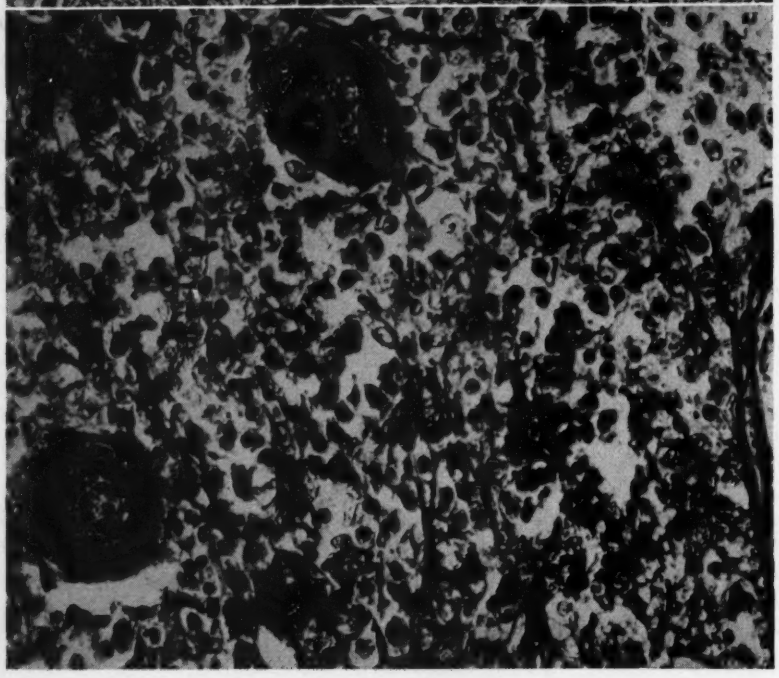


Fig. 6.

Fig. 5.—Ulcerated submucous fibroid at midcycle. Bleeding and highly vascularized endometrial surface. (×50.)

Fig. 6.—Ulcerated submucous fibroid at midcycle. Veins and sclerosed arteries under the bleeding endometrial surface. Stroma with blood and plasmocytes. (×400.)

In this case, the blood loss was from the fibroid. The endometrial ulcerated surface appeared to be a passive reservoir of blood with noncontractile and oozing vessels. In the case here reported, mechanical injuries and infection were added to the cyclical peaks of uterine congestion occurring in the fibroid throughout the menstrual cycle.

In other cases some aspects showed the transition between the congestive atrophic mucosa and the ulcerated fibroid. The edematous stroma of the former appeared progressively less edematous and more fibrous, becoming barely recognizable between the fibroid and the superficial epithelium. The fibroid might be called "subepithelial." The superficial epithelium itself was found to be normal and sometimes ciliated (Fig. 7). The presence of infection was not constant in these cases of ulcerated and subepithelial fibroids.

Fig. 7.—Subepithelial fibroid at midcycle. Ciliated superficial cells; hemorrhage by diapedesis from a narrow sinus through the epithelium. (×400.)

Summary and Conclusion

1. The material for this study has been selected in order to emphasize the influence exerted by submucous fibroids on menstruation. Any interference by important systemic, pelvic, or dyshormonal diseases able to disturb menstrual bleeding was avoided.

2. Perfectly normal menstruation was found in the cases where a mucosa with normal vascular pattern was seen above the fibroid.

3. In cases of menorrhagias or of metrorrhagias with recognizable menstruation, the mucosa lying above the fibroid was seen to be congestively atrophic or the myoma was found to be ulcerated. There was a transition between the normal and the congestive atrophic mucosa, and between the latter and the ulcerated fibroid. The coiled arteries disappeared and were replaced by small isolated sclerotic arteries while the amount of blood in the veins and sinuses was increased. The atrophic mucosa lying above submucous fibroids was likely to bleed longer than the normal surrounding endometrium, because of venous congestion and arterial defect. Ulcerated fibroids bled directly into the uterine cavity and showed similar vascular lesions.

In conclusion, submucous fibroids were covered by all types of endometria and the structures of these endometria and especially their vascular patterns could be correlated with the normal and pathological types of bleeding. The

presence of venous congestion and of arterial injury in cases of menstrual disorders fits well with the known data about the hemostatic mechanism of normal menstruation.

There is no doubt that functional hemorrhage may accompany submucous fibroids. Among cases which did not fulfill the criteria to be selected in this material, cystic glandular hyperplasia has been found above submucous fibroids. But this paper has shown that there was also an organic explanation for the bleeding in cases of nonulcerated submucous fibroids as well as in cases of ulcerated myomas. Large sinuses, described by Frankl, have been confirmed in the description of the congestive atrophic mucosa but stress has been laid also on the disappearance of the coiled arteries and on the sclerosis of the basal arteries. As to the anemic mucosa described by Sampson and by Faulkner on injected material, it might correspond to the pictures of some subepithelial fibroids or it might be correlated with the difficulty of the injection itself.

The author is greatly indebted to Dr. Howard C. Taylor, Jr., and to Dr. Earl T. Engle, Professor of Anatomy in the Department of Obstetrics and Gynecology, College of Physicians and Surgeons, Columbia University. Dr. Engle, whose many kindnesses the author wishes to acknowledge, assembled most of this material through a period of years and made this study possible by his valuable suggestions, his constant interest, and his active help.

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622 West 168th Street

PRESACRAL EPIDERMOID CYSTS IN WOMEN

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CONGENITAL presacral epidermoid cysts, despite their great rarity, comprise an important and interesting group of pelvic tumors. They are of particular concern to gynecologists, obstetricians, proctologists, and pathologists. They are not to be confused with the sacrococcygeal teratomas ("dermoids," "teratoids," and "fetal parasites") of infancy and childhood, which are composite solid or cystic tumors derived from more than one germinal layer. The general subject of presacral tumors has recently been reviewed by Jackman and associates.[1] Ectopic pelvic kidney has advisedly been deleted from the present paper, because no case has been encountered lying low enough to be considered actually in the presacral or retrorectal space. What follows is an inquiry into the congenital presacral epidermoid cyst. Three recent instances encountered in obstetrical practice are reported.

Anatomy of the Retrorectal Space

A description of the retrorectal space is essential to an understanding of presacral cysts (Figs. 1 and 2). The retrorectal space is but one compartment in the extensive extraperitoneum, where the cellular tissue of one region is continuous with that of another. This anatomical fact has been vividly demonstrated by the technique of extraperitoneal pneumography, where generalized subserous emphysema results from the injection of oxygen at low pressure into the tissues lying between the coccyx and the rectum.[2, 3]

The retrorectal space is a potential space, which is best delineated when the rectum is displaced anteriorly by a tumor (Fig. 3). This extraperitoneal compartment is bounded anteriorly by the rectum and posteriorly by the sacrum. It is delimited superiorly by the peritoneal reflection of the rectum, which is usually at the junction of the second and third sacral segments. The levator plate constitutes the floor or inferior boundary. Laterally, the retrorectal space extends beyond the anterolateral ligaments of the rectum to the lateral pelvic wall. The space is composed of areolar tissue, and normally contains branches of the sacral and sympathetic plexuses, the middle sacral and iliolumbar vessels and lymphatics.

Pathology of Presacral Cysts

Congenital presacral epidermoid cysts are lined with squamous epithelium and may contain sebaceous and/or apocrine glands, but hair and hair follicles are notably absent. The lining membrane is supported by a surrounding capsule of fibrous connective tissue. The cyst fluid may be clear or opalescent, thin or grumous, but hairs are absent. Granulation tissue is present if the cyst has recently been suppurative. From a histological standpoint these cysts resemble the anal canal, which is not lined by mucous membrane, but by squamous epithelium. The squamous epithelium of the anal canal normally

contains apocrine and sebaceous glands, which stop just external to the squamocolumnar junction. Hair follicles are not observed in the epithelium of the anal canal.

These simple epidermoid cysts are obviously different from the sacrococcygeal teratomas of infancy and childhood, classically described by Middeldorpf[4] in 1885. Teratomas are often discovered at birth, when the infant may present a sacculation posterior to the buttocks. The present writer can recall one such teratoma which caused serious dystocia in delivery of the trunk. Teratomas have variously been called "dermoids," "teratoids," "included twins," and "fetal parasites," but are preferably grouped together under the rubric of "sacrococcygeal teratoma."[5] Unlike the congenital presacral epidermoid cyst, the sacrococcygeal teratoma is trigerminal in origin, and, on adequate microscopic examination, may show derivatives of all three germinal layers, although elements of one layer may predominate. Although malignant change has not been recorded in presacral epidermoid cysts, Gross and associates[5] observed it in over 25 per cent of their series of 40 cases of sacrococcygeal teratoma.

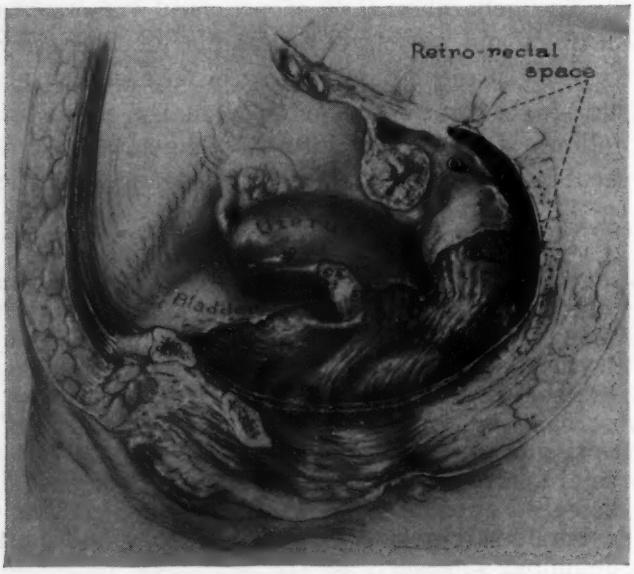

Fig. 1.—Parasagittal section through female pelvis to demonstrate extent and relations of retrorectal space. The rectum is drawn forward by traction hooks.

A third congenital anomaly which should be mentioned is the anterior sacral meningocele. It is an anterior meningeal herniation which is made possible by a sacral defect (anterior spina bifida or abnormally large sacral foramina). This anomaly is often associated with scimitar sacrum, and a total of 25 instances has been recorded.[6] Because of its direct connection with the subarachnoid space, compression of an anterior sacral meningocele will be reflected by a rise in spinal fluid pressure. Ill-considered incision or needling is, of course, liable to cause fatal meningitis.

Embryological Considerations

In several patients with presacral epidermoid cysts Scarborough[7] has noted a small opening in the posterior anal canal, 1 cm. external to the mucocutaneous junction. It is known that the anal canal develops from the canal-

ization of the *anal plate,* or posterior part of the cloacal membrane. It is Scarborough's opinion[8] that presacral epidermoid cysts develop from an offshoot of cells from the primitive anal plate which are detached when the plate undergoes canalization. The cyst fluid which eventually forms probably results from the secretory activity of the buried sebaceous and apocrine glands. It is quite plausible that this tell-tale opening in the posterior anal canal is a pathway over which infection reaches a presacral epidermoid cyst.

The sacrococcygeal teratomas probably arise from totipotent primitive cells. According to Gross and co-workers[5] the greatest concentration of such cells occurs in two areas: (1) the "primitive knot" (Hensen's node), which is finally located at the coccyx, and (2) the gonad anlage. A plausible explanation for the greater frequency of sacrococcygeal teratomas in females is the fact that the ovary, in requiring 5 to 15 days longer than the testis to develop, affords that much additional time for primitive genital cells to become ectopic.

Fig. 2.—Barium enema in normal female subject, aged 32 years. The retrorectal space is clearly outlined by the sacrum behind, the posterior rectal wall in front, and the peritoneal reflection above.

Symptoms and Signs

It is noteworthy that most epidermoid presacral cysts remain dormant for years before they become symptomatic. Such a cyst may rupture into the rectum during parturition or the passage of a hard fecal mass. Such a cyst may grow vertically and dissect upward behind the pelvic peritoneum, so that it may present above the pelvic brim. It is evident how such a cyst might be mistaken for an ovarian or parovarian cyst, or for an intraligamentary myoma. A presacral epidermoid cyst may be unexpectedly discovered (Case 2) during digital examination of the rectum to note the progress of labor.

A presacral epidermoid cyst may become infected and proceed to suppuration without specific antecedent trauma. Perhaps infection reaches the cyst

via the small telltale opening in the posterior median line of the anal canal, as described by Scarborough,[7] or by the perirectal lymphatics. Such a suppurative cyst may rupture internally and drain into the rectum, or externally in the postanal skin. In fact, the possibility of such a cyst should be considered in any patient with a history of recurrent abscesses or sinuses in or about the anus. It should be emphasized, however, that presacral cysts are prone to suppurate from trauma, diagnostic needling, and incision and drainage. Case 3 illustrates how the trauma of vaginal delivery may be followed by postpartum suppuration of a hitherto asymptomatic cyst.

Fig. 3.—Presacral tumor demonstrates expansion of retrorectal space and forward displacement of rectum.

Digital examination of the rectum is essential if one is to diagnose a presacral cyst. On vaginal examination alone one may easily overlook a retrorectal cyst. On digital examination of the rectum a presacral epidermoid cyst is found to be a smooth globular cystic tumor, which is fairly well fixed to the surrounding structures in the retrorectal space. Unless inflamed or recently traumatized, it is typically painless and nontender to palpation. Inspection may show the embryonic opening in the posterior median line, and forward displacement of the posterior rectal wall. In contrast to chordomas and other malignant tumors of the presacral space, the simple epidermoid cyst does not cause pain (unless infected), constipation, urinary retention or incontinence, or paresthesias, because there is no involvement of sacral nerve roots. X-ray visualization of the rectum may demonstrate its forward displacement by the space-occupying cyst (Fig. 4).

The differential diagnosis of a presacral mass, whether cystic or solid, requires a thorough investigation, as the possibilities are manifold.[1] However, space does not permit a recapitulation at this time.

Treatment

Presacral epidermoid cysts should be removed electively, because of the risk of suppuration and the possibility of causing dystocia. Moreover, be-

cause so many different lesions may occur in the retrorectal space, and inasmuch as so many of them are malignant, surgical extirpation is indicated even though the preoperative diagnosis is (benign) epidermoid cyst.

The recommended treatment for nonsuppurative presacral epidermoid cysts[9] is surgical extirpation after proper preparation of the bowel. Because of the frequency with which these cysts are intimately attached to the musculature of the rectum, and because of the inherent risk of opening the rectum, it is advisable to prepare the patient for several days as for bowel resection. The operation is most conveniently done under low spinal anesthesia, with the patient in the jackknife position. A longitudinal parasacral incision, which includes removal of the coccyx, is used. Ideally the cyst is removed extrarectally by sharp and blunt dissection. If total extirpation is impossible because of previous inflammatory reaction, as much as possible of the lining membrane must be curetted away. If any event the wound is packed open with petrolatum gauze.

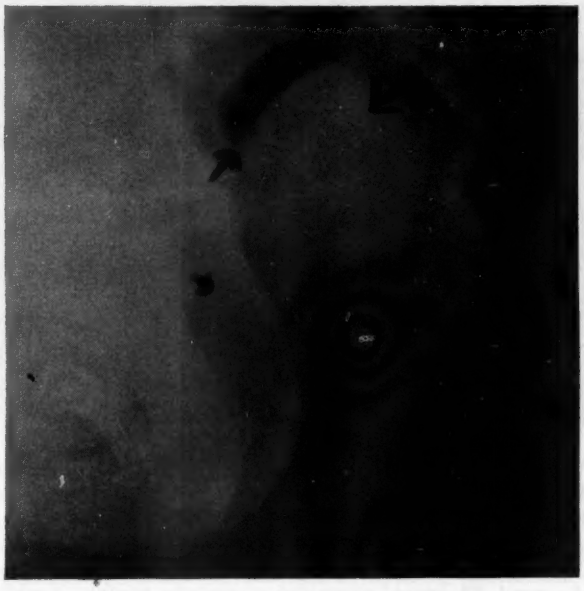

Fig. 4 (Case 2).—Lateral view of pelvis by soft tissue technique. Arrows indicate outline of presacral epidermoid cyst. The presence of gas in the rectum shows its extreme upward displacement by the cyst.

If the patient is first seen with an acute suppurative postrectal cyst it must be treated as any other abscess. Incision and external drainage are accomplished through a posterior parasacral incision and the cavity is packed open. Surgical extirpation of the cyst should be deferred until all signs of acute inflammation have subsided.

Presacral epidermoid cyst coincident with pregnancy poses several problems: If such a cyst appears to be so large that there is reasonable expectation that it would be traumatized during delivery, or that it would be a cause of dystocia, it is the writer's opinion that it should be electively removed, preferably during the middle trimester of pregnancy. If the cyst is first detected during labor, the obstetrician should carefully evaluate the fetopelvic relationship. If he is reasonably sure that the cyst presents no obstruction to vaginal delivery, then the proper course is easy pelvic delivery, avoiding all unnecessary manipulation. On the contrary, cesarean section is

clearly indicated if there is reasonable doubt as to the feasibility of vaginal delivery. Surely no surgical attack should be made upon a presacral cyst at the time of cesarean section. Should one attempt operative pelvic delivery, but find it impracticable, he should desist and proceed with extraperitoneal cesarean section.

The puerperium may be complicated by a suppurative presacral epidermoid cyst, which was traumatized by labor. Such an abscess may dissect extraperitoneally around the rectum, and present at the upper extremity of the rectovaginal septum (Case 3). Without doing a digital examination of the rectum the obstetrician might mistake this for an ordinary cul-de-sac abscess, and overlook the primary process in the retrorectal space. Incision and drainage (postrectally or per vaginam) at the point of maximal fluctuation is the indicated treatment.

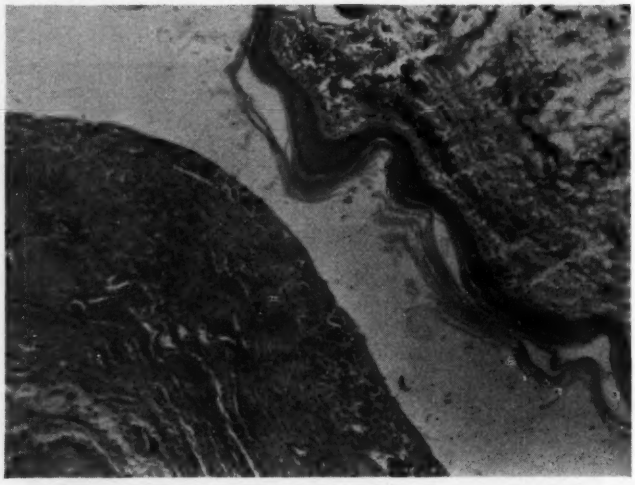

Fig. 5 (Case 2).—Photomicrograph of cyst wall. Note lining of stratified squamous epithelium covered by laminated keratinized material. There are numerous giant cells of the foreign body type, but no skin appendage structures are seen.

Case Reports

CASE 1.—M. J., aged 22 years, presented a septate vagina, double uterus and cervix. During the third month of her first pregnancy she drained pus per rectum. On digital examination of the rectum a finger could be inserted into a retrorectal pocket from which exudate drained. Proctological consultation suggested a retrorectal cyst. Pregnancy was otherwise uneventful, and the patient went into labor prematurely at 7½ months. Delivery of a viable infant who weighed 5 pounds, 1 ounce (2,296 grams) was effected by low forceps, after a three-hour labor. The puerperium was uncomplicated, and four months post partum a presacral epidermoid cyst was removed by the posterior extrarectal approach. Convalescence was normal, and the postoperative result was satisfactory.

CASE 2.—E. J., 35-year-old primigravida, experienced an uneventful pregnancy and went into labor at term. Past history was negative for anorectal disease. After a first stage of labor of seven hours, the vertex was engaged in left occipitoanterior position, and digital examination of the rectum disclosed a presacral cyst approximately 10 cm. in length by 6 cm. in width which occupied the retrorectal space, and displaced the rectum anteriorly. On performing the Hillis maneuver the examiner could be sure there was no cephalopelvic disproportion, as the vertex could be delivered past the presacral cyst. After a second stage of 90 minutes, delivery was effected by low forceps and episiotomy. The infant weighed 8

pounds, 8 ounces (3,856 grams) and appeared normal. Digital examination of the rectum immediately following delivery showed no change in the configuration or consistency of the retrorectal cyst. The puerperium was afebrile and uncomplicated.

Three months post partum the patient was admitted to the hospital for excision of the presacral cyst. She was prepared by low-residue diet and antibacterial therapy for five days preoperatively. Under low spinal anesthesia, a presacral cyst measuring 12 by 5 by 3 cm. was excised through a right parasacral approach, which included coccygectomy. Histological examination (Dr. David A. Wood) showed a typical epidermoid presacral cyst. The lining consisted of a flat layer of stratified squamous epithelium, covered by laminated keratinized material. Giant cells of the foreign body type were identified, but no skin appendage structures were noted (Fig. 5).

The postoperative course was afebrile and uncomplicated, and the patient was dismissed well on her eighth postoperative day. Follow-up examinations have shown a well-healed scar and normal pelvic contents.

CASE 3.—S. M., aged 26 years, had no anorectal symptoms until two months after her second parturition, when she gradually developed severe pain posterior to the anus. The pain was unrelated to bowel movements, and there was no rectal bleeding, or external swelling. Posterior colpotomy by the attending obstetrician yielded "one quart of pus" with immediate relief of pain for two days. A second colpotomy was done soon again because of recurrent pain. A rubber drain was left in the incision for 8 days, after which the vaginal opening healed, and did not reopen or drain pus, fecal material, or gas.

Several weeks after the vaginal drainage ceased there was recurrence of the pain posterior to the anus, and the patient was referred to a general surgeon, who diagnosed a huge inflammatory mass posterior to the rectum, extending up into the hollow of the sacrum and displacing the rectum forward. Incision was made posterior to the anus and an abscess containing one quart of foul-smelling pus was entered. Subsequently the abscess cavity was irrigated twice daily through an inlying catheter, and a large pad had to be worn at all times because of the odoriferous drainage.

Ten months later the patient was examined by Dr. Scarborough, whose diagnosis was congenital presacral epidermoid cyst, with secondary infection. After careful preoperative preparation of the bowel, a presacral cyst 10 by 4 by 6 cm. was excised through the usual posterior parasacral approach. The cyst was readily mobilized from the anterior wall of the sacrum, but was adherent to the musculature of the rectal wall. The full thickness of the cyst wall was removed up to 3 cm. of the dome of the cyst, where further dissection was thought to be too hazardous, because of the risk of opening the rectum or peritoneal cavity. The wound was left open, with petrolatum gauze packing. The patient was dismissed from the hospital on the twenty-second postoperative day with a granulating wound. The tract slowly healed from the inside out, and the sinus was completely closed and no cystic swelling could be felt rectally by six months following operation. There have been no recurrent symptoms, and the patient's condition remains satisfactory.

Histological examination (Dr. David A. Wood) described a typical presacral epidermoid cyst, the lining consisting of nonkeratinized stratified squamous epithelium, with leukocytic infiltration of the subepithelial tissues. The wall of the cyst contained bundles of rather large smooth muscle fibers.

Summary

The congenital presacral epidermoid cyst is an exceedingly rare pelvic tumor. It is a type of inclusion cyst, which probably results from cells which are detached from the anal plate, when the latter is canalized to form the anal canal. Such a cyst may remain silent for years, to be unexpectedly encountered at the time of labor or a pelvic laparotomy. Being prone to suppuration, such a cyst may be converted by infection into an abscess. Digital examina-

tion of the rectum is essential to diagnosis. The ideal treatment is elective total extirpation through a longitudinal parasacral incision, which includes coccygectomy. An infected cyst should be treated by incision and drainage. From an obstetrical standpoint, most patients may safely be delivered per vaginam, although cesarean section is indicated in the event of dystocia.

The author wishes to express his indebtedness and gratitude to Dr. Robert A. Scarborough for his liberal help, and elucidation of the proctological matters relative to this article. Appreciation is due Dr. Russell R. Klein for his constructive criticisms.

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490 Post Street

RUPTURE OF THE LIVER IN PREGNANCY: A RARE COMPLICATION OF ECLAMPSIA

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SUBCAPSULAR hematoma of the liver may result from the hepatic lesions of eclampsia. Rupture of Glisson's capsule from massive hemorrhage is one of the rarest complications of the disease. This accident of pregnancy presents a characteristic clinical picture and a very grave prognosis. The precise number of previously recorded cases must be few, since we have been able to find references to only 12 instances of rupture of the liver during pregnancy. To these we add the following case.

Case Report

The patient was a 31-year-old former nurse. Her only previous pregnancy, in 1944, was complicated by a nonconvulsive toxemia and resulted in a vaginal delivery at term of a male infant, who died at the age of 6 years of fibrocystic disease of the pancreas. The patient had moved in the meantime to Florida, where she was attended by a local physician during most of the current pregnancy.

Conception occurred on Nov. 14, 1950; the expected date of confinement was Aug. 7, 1951. The patient denied all illnesses except diaphragmatic pleurisy several years ago and measles as a child. She stated that her blood pressure prior to her first pregnancy was 90/70. Early in the sixth month of the present pregnancy she began to notice small bright spots before both eyes and to show other evidence of toxemia. The blood pressure was 130/80, the weight had increased from 154 pounds to 191 pounds, and the urine contained 2 plus protein. During the next four weeks the blood pressure fluctuated, going as high as 170/100, generalized edema developed, massive proteinuria appeared, and the weight increased to 195 pounds. The only treatment given was a mercurial diuretic, which resulted in transitory losses of weight which were regained overnight.

The patient then left Florida with her husband and spent the next four days motoring to New York, for continuation of obstetrical care and delivery. During the trip she complained of severe frontal headache and spots before the eyes. When first seen in New York, at noon on June 20, 1951, the patient complained of epigastric pain which had appeared that morning, massive generalized edema was present, the weight was 197 pounds, and the blood pressure was 220/140. She was admitted to the hospital immediately and put to bed at 12:30 P.M. Ophthalmoscopic examination of the retina showed moderate tortuosity of the arterioles and occasional areas of spasm. One small recent hemorrhage was seen in the right eye. Neither edema nor exudate was detected. The lungs were normal. The heart was normal except for accentuation of the second aortic sound. The epigastrium was tender but the liver could not be felt. The uterus was abnormally small for the duration of the pregnancy, extending to only two fingerbreadths above the umbilicus. The fetal heart was audible and regular in the right lower quadrant. Neurological examination was limited to testing of the patellar reflexes, which were markedly exaggerated.

The blood hemoglobin concentration was 15.3 Gm. per 100 c.c. The white blood cell count was 19,100, the polymorphonuclear leukocytes 77 per cent, lymphocytes 20 per cent, monocytes 3 per cent. The hematocrit was 42.9. The urine had a specific gravity of 1.018,

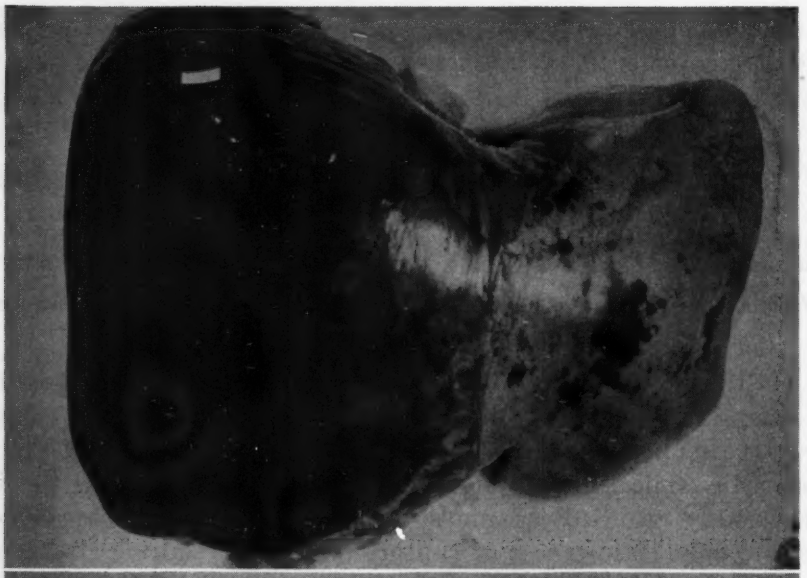

Fig. 1.

Fig. 2.

Fig. 3.

Fig. 1.—Liver, anterior aspect.
Fig. 2.—Liver, posterior aspect.
Fig. 3.—Liver, cross section.

was acid, gave a negative reaction for reducing substances, and contained 4 plus protein (7.8 Gm. Esbach). Microscopic examination revealed occasional red and white blood cells and many fine and coarse granular casts. The venous pressure was 120 mm. of saline.

During the next four hours the patient received, at intervals, morphine sulfate, magnesium sulfate intravenously, and chloral and potassium bromide mixture, but vomited the last. Four and one-half hours after admission (5 P.M.) she suddenly had a generalized convulsion which lasted about two minutes, following which the blood pressure was 240/120 and the patient remained unconscious. Oxygen was administered, magnesium sulfate was repeated, and the blood pressure declined to 170/115. During the next hour and a half the blood pressure was maintained at that level. At 6:30 P.M., while still stuporous, the patient complained of pain in the left shoulder. The blood pressure was still 176/120. One-half hour later the patient went rapidly into shock with mounting pulse rate, declining blood pressure, increasing respirations, and marked restlessness. She died undelivered at 7:30 P.M., two and one-half hours after the convulsion.

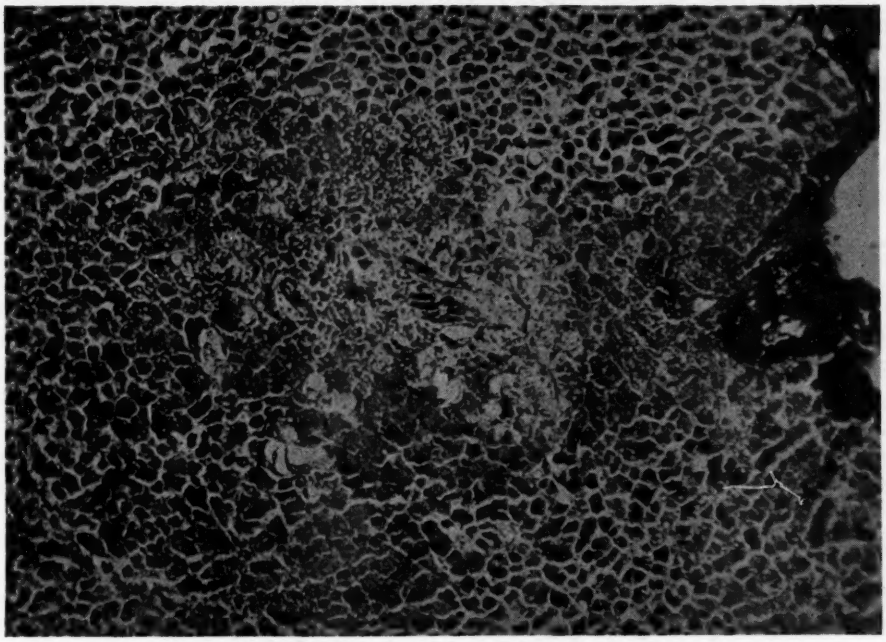

Fig. 4.—Histologic section of liver, showing necrosis.

At autopsy the peritoneal cavity contained 2,500 c.c. of fresh blood, mostly fluid. The liver weighed 2,100 grams. The left lobe was covered with multiple, irregular subcapsular hemorrhages. On the superior surface of the right lobe the capsule had been dissected completely free of the underlying liver by a layer of dark red fluid blood, but the area of rupture was not definitely established (Figs. 1 and 2). On section the parenchyma contained numerous scattered hemorrhagic areas which varied to about 1 cm. in diameter (Fig. 3). A small amount of blood was also present in the peritoneum overlying the anterior surface of the pancreas. The heart weighed 290 grams and was normal. The aorta was elastic. The kidneys weighed 150 grams each and the capsules stripped easily. The uterus contained a dead male fetus which weighed 1,400 grams. The placenta was intact and attached to the anterior wall of the uterus. No areas of infarction or hemorrhage were noted. The spinal fluid was clear. Histologic examination showed isolated, occasionally confluent, areas of hemorrhagic necrosis throughout the parenchyma of the liver. These were chiefly in the portal areas, characteristic of eclampsia (Fig. 4). The glomerular tufts of the kidney were swollen, with thickening and hyalinization of the basement membrane. Trophoblastic emboli were present in the small blood vessels of the lung. In view of the history of fibrocystic disease in the previous offspring it is of interest that the fetal pancreas was normal.

TABLE I. RUPTURE OF THE LIVER IN PREGNANCY

AUTHOR	(YEAR)	AGE OF PATIENT (YEARS)	GRAVIDA	DURATION OF PREGNANCY	TOXEMIA	CONVULSIONS	VOMITING	TRAUMA	PAIN	RESULT
Abercrombie[1]	(1844)	35		Term			+	+	+	Fatal
Kosoloff[7]	(1914)	39	Primi-		+					Fatal
Herz[5]	(1918)	41	Multi-	8 months	+	+			+	Fatal
Kolisko[6]		24		Term	+	+		?		Fatal
Duverges[3]	(1928)	39	Multi-	Term	+	+	+		+	Fatal
Roblee[11]					No Details					Recovery
Roemer[12]	(1941)	30	Multi-	7 months	+	+			+	Fatal
Rademaker[10]	(1943)	32		8 months	+		+		+	Recovery
Sanes and Kaminski[13]	(1946)	26	Multi-	7 months	+	+				Fatal
Links[8]	(1946)	42	Multi-	16 weeks					+	Recovery
Burton-Brown and Shepherd[2]	(1949)	32	Multi-	Term	+		+		+	Recovery
Haller[4]	(1951)	34	Multi-	38 weeks	+				+	Fatal
Present case		31	Multi-	7 months	+	+	+		+	Fatal

Comment

Rupture of the liver is almost always the direct result of trauma. Spontaneous disruption of this organ is extremely rare. Yet, of the few reported cases in pregnant women only one was clearly traumatic. This was Abercrombie's[1] patient, who applied a kerchief around her abdomen and had a servant pull it tight in an effort to provide relief from epigastric distress. Several hours afterward labor ensued and the patient had a normal delivery. Collapse occurred within the next hour and death followed 26 hours after delivery. At autopsy there was a large amount of free blood in the peritoneal cavity and two lacerations in the liver. Even in this case the absence of adequate data does not exclude the possibility of toxemia of pregnancy.

An attempt has been made by some to invoke trauma as an explanation for the accident in other cases but such explanations seem farfetched and unconvincing. Kolisko,[6] for example, reported that his patient had been scrubbing the floor prior to her collapse, and he surmised that she had suffered some injury as a result. Far more striking, however, than the possibility of trauma is the observation that all but two of the cases of hepatic rupture in pregnancy occurred in conjunction with toxemia, and six of the patients are known to have had convulsions. The combination of hypertension, convulsions, and vomiting, which is also known to have occurred in several patients, is apparently adequate to raise the intra-abdominal pressure to the point of rupture of Glisson's capsule by a massive hematoma which has resulted from the liver lesions.

In contrast to the young primipara, who is the eclamptic prototype, all but one of the patients of known parity who had spontaneous rupture of the liver in our collective series were multiparas and their average age was 34 years (Table I). This is in keeping with the occurrence of spontaneous rupture of the uterus in pregnancy and suggests the possible importance of degenerative changes in the connective tissue as a result of aging.

Eclamptic patients are notorious for their tendency to spontaneous hemorrhage. In addition to the common hemorrhagic lesions of the liver and the high incidence of premature separation of the placenta, many suffer hemorrhage into the subarachnoid space[14] and into the brain. Welch's[15] patient had such a lesion in addition to her hepatic accident; and the patient reported by Sanes and Kaminski[13] also had a spontaneous hemorrhage into the rectus muscle. Rupture of the spleen has likewise been observed, and Ogden[9] has recently reported a fatal case of retroperitoneal hemorrhage from the pancreas. Current researches on the pathological physiology of eclampsia suggest the importance of fibrinogen depletion in these hemorrhagic phenomena.

Severe pain under the right costal margin has been a prominent part of the clinical picture in most of the reported cases of hepatic rupture and led in several to the diagnosis of biliary colic. The rapid development of shock in a toxemic patient with epigastric, right upper quadrant, or shoulder pain should suggest the possibility of this accident. Despite the grave prognosis which must accompany rupture of the liver in pregnancy, it is of some encouragement to note that four patients (2, 8, 10, 11) recovered following abdominal operation.

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THE ABUSE OF ESTROGENS IN THE TREATMENT OF LEUKOPLAKIA OF THE VULVA

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THE reports in the medical literature dealing with the management of leukoplakia of the vulva indicate a lack of agreement. One of the factors probably responsible for this rather confused situation is the obscured etiology of this disease. As a result, the medical profession as a whole has not seriously appraised the cancer potentiality of this malady.

My interest in developing this study stems from these clinical observations: first, the age incidence of women afflicted with leukoplakia of the vulva; second, an increased incidence of carcinoma coexisting with leukoplakia of the vulva in this same age group of women; third, the abuse of estrogens in the treatment of leukoplakia of the vulva, with presentation of a case under treatment with stilbestrol and under observation before the development of cancer.

Material

A review was made of 34 cases of leukoplakia of the vulva in patients admitted to the Roswell Park Memorial Institute during the years 1918 to 1948, inclusive. This study shows that most of the patients were either in the menopause or were postmenopausal, as shown in Table I, *A*. The average age is approximately 58.4 years which is slightly higher than the average age of 50 years indicated in other reports.[1] The greatest occurrence as shown is in the fifth decade. All patients were white with the exception of one who was Negro. The youngest patient was 30 years and the oldest patient 78 years of age. Severe pruritus and burning after urination were common complaints in all but three in this group. The duration of symptoms varied from 3 months to 30 years before admission, and 85 per cent had the symptoms lasting three months or more. All received symptomatic care before admission with various medicaments by local, oral, or parenteral administration. In 2 patients a definite history of the use of estrogens in addition to other therapy was recorded, but the entire group of 34 patients suffered from symptoms of the menopause, 8 from surgical menopause and 26 from natural menopause as shown in Table IV. In 12 (35.3 per cent) of the 34 cases there was found a coexisting carcinoma of the vulva in a leukoplakic basis as shown in Table I, *B*. (Recent reports in the literature indicate that this associated malignancy varies from 21.3 per cent to 55 per cent.) In 5 (41.6 per cent) of the 12, carcinoma occurred in the age period of 51 to 60 years. One patient had a leukoplakia of the mouth associated with that of the vulva. Kraurosis vulvae as an associated disease was present in 10 (29.4 per cent) of the 34 patients. One patient in the fifth decade had carcinoma of the breast associated with leukoplakic vulvitis.

TABLE I. LEUKOPLAKIA OF VULVA (34 CASES)

AGE DECADES (YEARS)	A NUMBER	A PER CENT	B ASSOCIATED VULVAR CARCINOMA NUMBER	B ASSOCIATED VULVAR CARCINOMA PER CENT
21-30	1	2.9		
31-40	4	11.8		
41-50	3	8.8	1	
51-60	11	32.3	5	
61-70	7	20.6	3	
71-80	8	23.6	3	
81-90				
Total	34	100.0	12	35.3
Average age 58.4 years				

A comparative study was also made of 33 cases of leukoplakia of the mouth in patients admitted during this same period. The purpose of this study was to detect any differential factors that might exist in relation to age, menarche, menopause, coexisting cancer, or associated leukoplakia and possible estrogenic influence of these two anatomical variations of the same condition. This study revealed that the average age of the patient with leukoplakia of the mouth was 52.3 years as shown in Table II, *A*, which is consistent with the average age of the vulva group of 58.4 years, in that the average age of both was in the fifth decade of life. The timing of the menarche and menopause in both groups was approximately synchronous as shown in Tables III and IV. On only one (3.0 per cent) of the 33 cases of leukoplakia of the mouth, a coexisting carcinoma in a leukoplakic basis was found as shown in Table II, *B*. One patient had leukoplakia of the vagina associated with that of the mouth. All suffered from menopausal symptoms. The majority had some form of vitamin B deficiency treatment.

TABLE II. LEUKOPLAKIA OF MOUTH (33 CASES)

AGE DECADES (YEARS)	A NUMBER	A PER CENT	B ASSOCIATED MOUTH CARCINOMA NUMBER	B ASSOCIATED MOUTH CARCINOMA PER CENT
21-30	0	0		
31-40	7	21.2		
41-50	9	27.3		
51-60	7	21.7		
61-70	9	27.3	1	
71-80	0	0		
81-90	1	3.0		
Total	33	100	1	3.0
Average age 52.3 years				

TABLE III

AGE AT MENARCHE (YEARS)	LEUKOPLAKIA VULVA (34 CASES)	LEUKOPLAKIA MOUTH (33 CASES)
11	2	1
12	3	6
13	7	9
14	10	7
15	2	5
16	9	4
17	1	1
Average age	13.1 years	13.7 years

TABLE IV

AGE AT MENOPAUSE (YEARS)	LEUKOPLAKIA	
	VULVA (34 CASES)	MOUTH (33 CASES)
30-34	2*	0
35-39	1*	3*
40-44	9 { 5* / 4	4
45-49	10	12
50-54	12	14
Average age	46.3 years	47.7 years

*Surgical menopause.

Comment

Two groups of cases with the same clinical manifestations of leukoplakia but involving two different anatomical sites were studied. In both groups no diversified peculiarities were found in respect to the average age, age at menarche, or at onset of menopause. One prominent disagreement was, however, noticeable in connection with the incidence of associated cancer in these two groups.

Twelve (35.3 per cent) of the 34 patients with leukoplakia involving the vulva had coexisting cancer and in only one (3.0 per cent) of the 33 patients with leukoplakia involving the mouth was coexisting cancer present. It is quite natural that this phenomenon should arouse interest and raise the question as to why leukoplakia of the vulva yields to malignant degeneration more readily than leukoplakia of the mouth. This writer's opinion is that the answer to the question may be found in the etiological consideration of the disease. A perusal of reports on leukoplakia of the vulva leads to an impression that deficient ovarian activity is the main etiological factor. The continued repetition in standard textbooks of gynecology[2] leads to a similar impression which I believe has been a strong influence for the abuse of estrogens in leukoplakia of the vulva and the high incidence of associated carcinoma. In considering the etiology of the leukoplakia of the mouth, on the other hand, the majority of the reports on the subject lay the emphasis on the faulty dietary assimilation or vitamin B deficiency as the main etiological factor. Thus, eliminating the abuse of estrogens in this condition, there was found a coexisting cancer in only one (3.0 per cent) of the 33 cases. The following case is presented to illustrate the abuse of estrogens in leukoplakia of the vulva.

Case Report

Mrs. M. J., No. 37688, a widow, aged 71 years, was admitted to the Roswell Park Memorial Institute on Dec. 29, 1942. Five years prior to her admission, an area on the vulva was coagulated and biopsied. Histological report received was chronic inflammation of the vulva. Intermittently since that time she had had episodes of itching and burning of the vulva with various forms of therapy. A diagnosis of leukoplakia of the vulva was made by the examining physician (not the author) and stilbestrol, 1 mg., was prescribed daily for a month.

Jan. 26, 1943: She complained of soreness, tenderness, and fullness of the breasts. The leukoplakia had markedly regressed. The itching and burning subsided. She had been taking two (1 mg.) pills a day instead of one pill as prescribed. She was advised to take only one (1 mg.) pill every other day (seen by the same physician).

Feb. 8, 1943: She returned before her regular appointment because of vaginal bleeding. The breasts were less sore. The leukoplakia was improved. The patient was admitted for dilation and curettage and the report on tissue removed was hyperplasia of the endometrium. Stilbestrol was discontinued (seen by the same physician).

April 5, 1943 (under care of the author for the first time): The vulva was much improved. There was very little itching or burning. The breasts were not sore.

June 29, 1943: There was no burning or itching. There was moderate vulvitis with some superficial keratosis of the epithelium in the inner vulva.

Oct. 19, 1943: There was a return of itching and burning. The patient had noticed a small nodule in the left vulva region, several days previously. Examination disclosed reappearance of leukoplakia. There was a small raised nodule in the left vulva, near the fourchette, about 6 mm. in diameter, keratotic and slightly adherent to underlying tissues. The lesion was excised under local anesthetic. The pathological report (Fig. 1) was squamous-cell epithelioma.

Nov. 10, 1943: The patient was admitted to the hospital and total vulvectomy was done. The histological report (Fig. 2) was squamous-cell epithelioma.

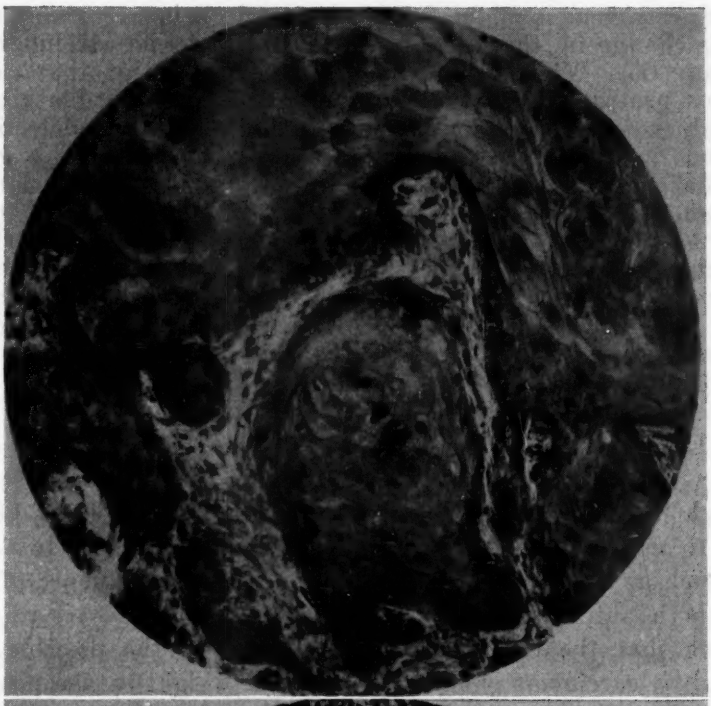
Nov. 27, 1943: The patient was discharged in good condition.

Since discharge, she was followed up and observed at the clinic at frequent intervals. During the last visit in January, 1949 (5 years and 2 months since vulvectomy), there was no recurrence of either the carcinoma or the leukoplakia. She had no complaints.

It has been the purpose of this case report to present the sequence of events leading to carcinoma of the vulva in a woman 71 years old under observation and treatment with stilbestrol for leukoplakic vulvitis of many years' duration. Although the possible carcinogenic role of estrogens in leukoplakia is far from complete, nevertheless, it is probably a sound policy to avoid giving any estrogenic hormone until future investigation and research produce more substantial evidence that estrogenic stimulation is not the initiating carcinogenic factor. Curtis[2] states that "the rather wide spread use of estrogens has demonstrated that it is useful in the therapy of this affection (leucoplakia of the vulva) but it is by no means a specific. The course of leucoplakia is usually slow but carcinoma may appear suddenly and develop rapidly, quite in contrast with epithelioma in other locations." I heartily agree with this statement and it is my experience that estrogenic therapy is useful and, may I add, beneficial, but the effect is only temporary and recurrence of the symptoms and of the leukoplakia is the rule. As it is stated in this case report, a carcinoma had appeared suddenly and developed rapidly and I see cause to believe that this change might be due to prolonged and indiscriminate use of estrogens and not be a result of chronic irritation or abnormal thickening or deformity of epithelium alone. The contribution of Miller[3] seems to dispute the concept that leukoplakia is associated with an estrogen deficiency. He bases his reasoning on studies and clinical observations that leukoplakia may exist without improvement in young women during pregnancy when the estrogen levels are normally high. In a urinary estrogen assay on 26 patients with leukoplakia of the vulva, Miller and coworkers found that 22, or 84 per cent, had normal or above normal estrogen excretion rates.

There is evidence that estrogens are now used widely for treatment in both leukoplakia and kraurosis vulvae and that the profession in general has not recognized the importance of these precancerous conditions. There is also evidence to support our concept that estrogens are unwisely used in menopausal therapy, a stage in which the age incidence of most of the women with leukoplakia of the vulva belongs. We see a large number in this clinic because of abnormal uterine bleeding induced by improper or prolonged dosages of estrogens. Since my original paper[4] on the clinical use of vitamin E in the menopause, in July, 1945, I have not employed any estrogens in any form as a therapeutic agent in women presenting symptoms of the menopause. Vitamin E has demonstrated its effectiveness now in a large number of patients and the results will be reported in the near future. Its chief ad-

Fig. 1.



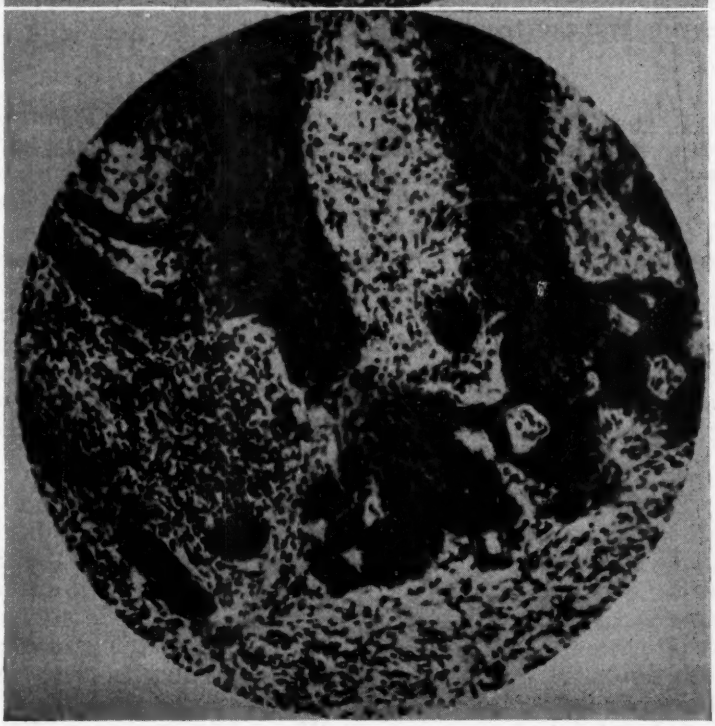


Fig. 2.

Fig. 1.—Section of tissue from the vulva showing a squamous-cell carcinoma of differentiated cell type with pearl formation; the material received consists entirely of tumor.

Fig. 2.—Section of tissue from vulvectomy shows marked thickening and hyperkeratosis of squamous epithelium. In some areas papillae are projecting downward for a considerable distance and islands of epithelial cells are found free in the submucous connective tissue. We are inclined to think that this represents a malignant change in the deeper layers of epithelium.

vantage over estrogens is in the fact that vitamin E is free of any stimulative effect on, or change in, the genital system and plays no carcinogenic role as estrogens may do. We know by animal experimentation that carcinoma is produced by protracted estrogenic injections on susceptible tissue. It is quite natural, therefore, that we should become interested in detecting parallel manifestations in the human being, even if a positive effect of a given chemical on animal tissue implies no assurance that a similar effect can be anticipated in man. It can readily be seen from this comparative analysis of the two groups of patients with leukoplakia that there is no incontestable proof that leukoplakia per se is the precursor of carcinoma. On the other hand, it is my firm belief that the controversial association of leukoplakia of the vulva with the development of vulvar carcinoma already commented upon in this case presentation is presumably a result of persistent estrogenic stimulation of the atypical leukoplakic epithelium and perhaps represents more than a mere histologic coincidence.

Conclusion

The high incidence of associated carcinoma in leukoplakia of the vulva in contrast to that of leukoplakia of the mouth may after all in a theoretical discussion such as this reflect the postulation that the influence of estrogenic stimulation is the initiating carcinogenic factor.

I believe that the consideration just given to the possible etiological factor of vulvar carcinoma should be given due weight by the physician who takes the responsibility of treating such a patient.

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ENDOMETRIOSIS OF THE VERMIFORM APPENDIX

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IT IS generally agreed that removal of the vermiform appendix is probably the most common operation in the field of intra-abdominal surgery. Increasing care in the pathological examination of surgical specimens during the last decade has led to increasing knowledge of diseases affecting this organ.

Pelvic endometriosis, although first reported and described by von Rokitansky in 1860, was brought to wide attention by Sampson in a life-long effort to prove his theory of retrograde, transtubal menstruation. Much literature and investigative work since then still leave doubt in the minds of both the pathologist and clinician about the true nature of this condition. The multiplicity of its reported aberrant locations, its reaction to hormones, and its secondary alteration of anatomy and physiology of many body organs have confused the proponents of every theory of pathogenesis. Explanation of endometrial tissue growth within the wall of the vermiform appendix will be left to the imagination of the reader.

In a review of the world literature Donald C. Collins recently collected one hundred thirty-four cases of endometriosis of the vermiform appendix as presented by sixty-four authors between the years 1860 and 1951. No single author has collected sufficient data concerning the clinical aspects of the disease to place it in any other category than that of a pathological curiosity. One of Collins' cases developed severe melena which subsided after removal of an appendix proved to be involved with endometriosis.

Even though the appendix is not uncommonly found lying with its tip in the true pelvis, it is not considered a common site for endometrial tissue growth.

A comparative analysis of the diagnosis and treatment of 866 cases of endometriosis, including fifty-three cases of intestinal endometriosis, as reported by Thierstein and Allen, revealed only two cases in which the appendix was involved.

Material

In a study of the records of patients operated upon since 1940, in three of the hospitals of the St. Louis University group, 15 cases of endometriosis of the vermiform appendix were found, divided as follows: Firmin Desloge Hospital had no such cases on record. There were 14 cases recorded at St. Mary's Hospital. The records at St. Mary's Infirmary (hospital for Negroes) revealed one case. During this period a total of 6,911 appendectomies were performed in all three hospitals. The incidence of proved endometriosis in this group is 0.0217 per cent. These fifteen cases will be analyzed from a clinical standpoint by dividing them into two groups:

A. Those in which the preoperative diagnosis was appendicitis, 2 cases.

B. Those in which the preoperative diagnosis was other pelvic or abdominal pathology and in which an incidental appendectomy was performed, 13 cases.

The cases in Group "A" will be presented with individual case histories while those in Group "B" will be discussed together.

Group A (Two Cases)

CASE 1.—This nulliparous Negro female, aged 19 years, was admitted to the hospital complaining of generalized abdominal pain, nausea and vomiting of twenty-four hours' duration. This was the first episode of gastrointestinal disturbance she had experienced except those associated with childhood diseases. The menstrual history was entirely normal with mild midline cramps the first day since its inception at age 13. The last menstrual period began ten days before the present illness and ended as usual, four days later.

On admission, abdominal examination revealed maximum tenderness at McBurney's point with right-sided muscle guard. Vaginal examination disclosed a uterus of normal size and position and no adnexal masses were palpable. Sublingual temperature was 98.4° F. White blood cell count was 8,400 with no shift, the urine was negative, nonprotein nitrogen 31 mg. per cent, and blood sugar 89 mg. per cent.

Under general anesthesia, a McBurney incision was made and the peritoneal cavity opened. No free fluid was encountered. The appendix lay free in the abdomen and was of average size. The surface was smooth and glistening. The right ovary was removed along with the appendix and the abdomen was closed. There were no postoperative complications.

This patient was interviewed by the author (C. E. S.) four weeks after surgery and she had a menstrual period identical to previous regular periods, except that it was of only three days' duration.

The photomicrograph shows the appendix in cross section (Fig. 1). Microscopic examination (courtesy of Dr. Vincent Moragues, Department of Pathology): "Several sections of the appendix revealed a normal intact mucous membrane. In the muscular coat there were many islands of endometrial glands and stroma. Some of the endometrial islands contained much blood and brown pigment within the glands. Some of the pigment was inside large phagocytes. There was no evidence of inflammation of the appendix. Sections from the right ovary revealed one small endometrial cyst."

CASE 2.—A nulliparous white woman, aged 24 years, became acutely ill with nausea and vomiting and generalized abdominal pain. She was placed in bed at home, put on a liquid diet for three weeks, and improved. Abdominal pain and nausea after eating persisted and she was therefore admitted to the hospital for further study. Her last menstrual period began six days after the onset of the present illness. Her menstrual history had always been normal and she had never complained of menorrhagia or dysmenorrhea. Appendectomy was performed through a McBurney incision and the postoperative recovery was uneventful. Microscopic examination of the appendix revealed active endometrial glands and stroma in the muscular coat in the subserosa.

Group B (Thirteen Cases)

These patients had no gastrointestinal symptoms.

It is not within the scope of this paper to consider all symptoms of endometriosis but the complaints of these thirteen patients will be briefly presented. Duration of symptoms varied from a few months to ten years:

NO SYMPTOMS	MENORRHAGIA	DYSMENORRHEA	LOW BACK PAIN	ABDOMINAL PAIN
1 Case	7 Cases	5 Cases	5 Cases	4 Cases

The patient with no symptoms was operated upon because examination revealed palpable nodules on the posterior surface of the uterus and third-degree retrodisplacement. In addition to the asymptomatic patient, four of the other patients in this group had third-degree retrodisplacement of the uterus.

There were associated uterine fibroids in six cases. Chronic cervicitis was present in three cases. The age incidence ranged from 26 to 50 years.

Conservative surgery was carried out as indicated, varying from suspension with incidental appendectomy to hysterectomy and partial removal of adnexa. In every case, some ovarian tissue was conserved.

It is interesting to note that the pathological report emphasized that the ectopic endometrial tissue was limited to the subserosal layer of the appendix in all thirteen cases. There was no penetration of endometrial tissue deep into the muscular coat.

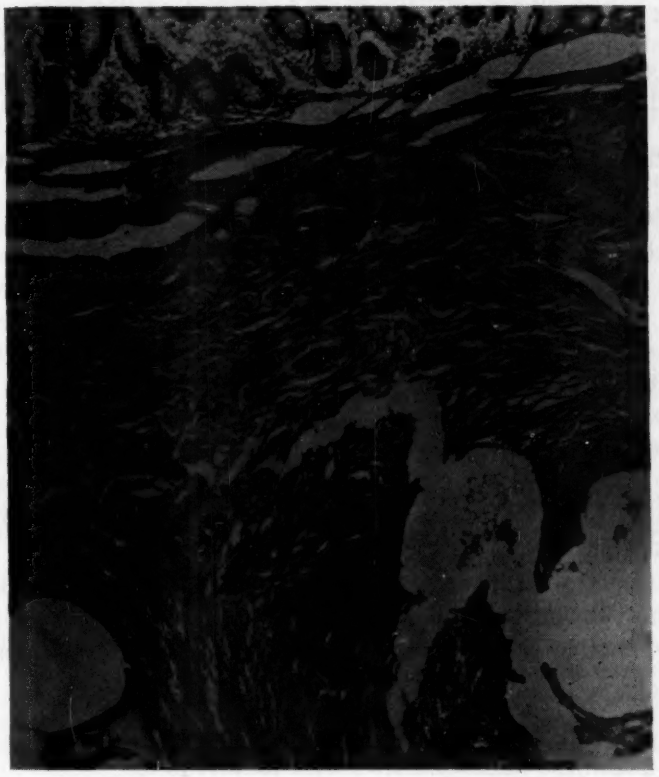

Fig. 1.—Endometrial glands and stroma deep in the muscularis of the appendix. (×100.)

Comment

Group A or those patients in whom the preoperative diagnosis was appendicitis: The first patient in this group was a 19-year-old girl who had endometrial involvement of the muscular coat of the appendix and presented the clinical picture of acute appendicitis.

This patient was very young for discovery or development of endometriosis. There are very few cases reported in the literature of endometriosis in patients under 20 years of age.

It is unusual that this patient had finished a menstrual period six days before she became ill, since, in most cases of endometriosis, the symptoms are worse during the menses.

In addition, since there was no free peritoneal fluid found at operation and since the temperature and leukocyte count were not elevated, it would be difficult to explain these sudden violent symptoms on the basis of peritoneal irritation.

And, finally, it is almost inconceivable that this aberrant endometrial tissue could be transferred to such a deep position within the muscularis of the appen-

dix and set up such violent symptoms in just a few hours. In this patient, there is some indication that endometriosis may have been present in the right ovary and appendix for some time without causing any distress at all.

The second patient in this group had symptoms of appendicitis yet at operation the appendix was not acutely inflamed. The time of onset and the duration of symptoms in this case are not characteristic of the pain of endometriosis. She had no previous gastrointestinal difficulty so that the amount of involvement does not parallel the symptoms produced.

Group B or those patients with a preoperative diagnosis of other pelvic or abdominal pathology and upon whom incidental appendectomy was performed: Not one of 13 patients with widespread endometriosis, including endometriosis of the appendix, had symptoms that could be confused with appendicitis.

The fact that deep muscular involvement was not present raises the question of whether involvement of the muscular coat with endometriosis may be the determining factor in the presence or absence of symptoms comparable to those of acute appendicitis. The number of cases presented is obviously too few to justify a definite statement in this regard.

Summary and Conclusions

1. Since 1940 there have been 15 proved cases of endometriosis of the vermiform appendix in the St. Louis University Hospitals.

2. Two of the cases clinically simulated acute appendicitis. Both of these cases presented endometrial tissue deep in the muscularis of the appendix.

3. In the other 13 cases of pelvic endometriosis with superficial involvement of the appendix, but without invasion of the muscularis, there were no gastrointestinal symptoms.

4. In patients with pelvic endometriosis, involvement of the vermiform appendix is not uncommon. It would therefore seem advisable, when surgery for pelvic endometriosis is undertaken, to perform incidental appendectomy.

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A FORMULA FOR SELECTING THE OPTIMUM TIME FOR CONCEPTION*

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MANY methods have been employed for determining the occurrence of human ovulation. These include the use of alterations in body temperature, changes in the cervical mucus, variations in the character of cells secured from vaginal smears, tissue from endometrial biopsies, increase in walking, electrometric determinations, and hormonal assays. All have their disadvantages, and none is very accurate. Recently, the rat ovarian hyperemia test has become available (Farris[1]), and offers perhaps the most accurate method. The present report deals with the use of this test in the timing of the ovulation of 148 women who conceived 150 times. The results permit the development of a formula for determining the optimum time for coitus or insemination for conception.

Materials and Methods

Observations were made upon three series of women. The first group of 50 women each supplied a record of the lengths of 12 or more consecutive cycles.

A second series of 48 women had a total of 50 conceptions, each resulting from insemination performed only once in the month.

A third series of 100 women each conceived once by coitus practiced only once during the fertile period.

The time selected for either the insemination or coitus was determined by the use of the rat hyperemia test described previously.[1-9] The data for series 2 and 3 are combined on account of similarity in the results.

Ovulation of each patient was timed for two consecutive months. The first month's timing was utilized as a control, and no attempt at conception was made during that month. This control month test indicates the presence or absence of normal ovulation activity, and approximately when in the month it takes place. Intercourse was advised, or artificial insemination was performed during the second month, if a normal ovulation reaction was recorded. No attempt at conception was planned if the reaction was abnormal, since conception has proved to be unlikely under such circumstances.[1, 7, 8]

Results

The Average Length of the Menstrual Cycle.—The average length of 12 consecutive cycles of each of 50 patients was computed for 3, 6, 9, and 12 month periods. Each average was expressed in whole days. If the average included a fraction of 0.5 or more days, a full day was added to the average. Any fraction less than 0.5 of a day was omitted from the average.

The average length of any 3 consecutive cycles was about the same length as the cumulative averages of that person for 6, 9, or 12 cycles. The maximum variation in the average of 3, 6, 9, or 12 cycles was not over 2 days in the majority of instances.

*This investigation was aided by a grant from the Samuel S. Fels Fund.

Eighteen per cent of the 50 women varied less than a day in the average length of 3, 6, 9, or 12 cycles. Fifty-two per cent varied 1 day, and 14 per cent varied 2 days. The majority, or 84 per cent, varied no more than 2 days.

The data indicate that the average length of any 3 consecutive cycles (expressed to the nearest whole day) varies so slightly from the average of more than 3 cycles, that only 3 consecutive cycles need be utilized to obtain a practical average.

Day for Successful Insemination or Coitus.—Table I reveals the days of successful insemination or coitus for the 148 women who conceived 150 times (series 2 and 3 combined). The selected day was determined by the use of the rat hyperemia test.

The greatest number of conceptions occurred when insemination or coitus was performed 2 days prior to the midcycle day. For example, in Table I, in the case of the 26 day cycle, 10 of the 27 conceptions occurred when insemination or coitus took place on day 11, which was two days before the midcycle day. The next largest number (six conceptions) took place when coitus or insemination was practiced one day before the midcycle day. The midcycle day itself was the third most successful day (5 conceptions). This is a total of 21 of the 27 conceptions, or 78 per cent, which took place during these three days.

TABLE I. DAY OF SUCCESSFUL COITUS OR INSEMMINATION IN RELATION TO DAY OF MENSTRUAL CYCLE (148 WOMEN HAVING 150 CONCEPTIONS)

AVERAGE LENGTH OF 3 CONSECUTIVE CYCLES*	NUMBER OF CONCEPTIONS	DAY OF MENSTRUAL CYCLE														
DAYS		8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
23	3					2	1										
24	7		2	3	2												
25	11		2	4	4				1								
26	27		2	2	10	6	5	1			1						
27	28	1		4	6	4	6	4	2		1						
28	25				5	8	6	3	2	1							
29	17			1	1	7	2	3	1	1	1						
30	9				1	2	2		3					1			
31	7					1			3	2		1					
32	6						2		2	2							
33	2								2								
34	4							1		2	1						
35	1																1
38	1													1			
40	1											1					
41	1											1					
Total	150																

The days of the above successful coitus or insemination were selected by the rat hyperemia test.

*Calculated to the nearest whole day.

Two conceptions occurred when insemination or coitus was practiced 3 days prior to the midcycle day, and one on the day after the midcycle day. An analysis of the remaining cycles shown in Table I reveals an equally high incidence of conceptions on the above-mentioned days.

These observations suggest three schedules for selecting the optimum time for insemination or coitus. The use of these schedules should always be preceded by 5 days' abstinence, so that the husbands will possess the maximum number of active sperm cells.[6]

The Formula

Schedule A.—

1. Average three recent, consecutive menstrual cycles, to the nearest whole day. A day is added if the fraction is greater than 0.5 of a day.

2. Divide this number by 2. Omit any fraction of a day.

3. Starting *2 days* before this midcycle day, practice coitus once daily for 3 consecutive days.

Schedule B.—

If conception fails after following Schedule A for four months:

Practice coitus, starting *3 days* before the midcycle day, daily for 3 consecutive days.

Schedule C.—

If conception fails after following Schedules A and B for four months each:

Practice coitus, starting *1 day* before the midcycle day, daily for 3 consecutive days.

There were 150 conceptions by timing ovulation with the rat hyperemia test (Table I). Of this number, by using Schedule A, 98 conceptions occurred as follows: 42 two days previous to the midcycle day; 30 one day before the midcycle day; and 26 on the midcycle day. These represent 65 per cent of the conceptions.

If coitus or insemination had been practiced by the women listed in Table I according to Schedule B rather than Schedule A, the first attempt 3 days previous to the midcycle day would account for 22 conceptions, with 42 and 30 more occurring on the next two days, for a total of 94 conceptions, or 63 per cent.

Finally, if coitus or insemination had been practiced by the women listed in Table I according to Schedule C, with the first attempt being made one day previous to the midcycle day, 30 conceptions would have occurred, with 26 and 13 more on the next two additional days, for a total of 69 conceptions, or 46 per cent.

Theoretically, then, if each of the 148 women had followed Schedules A, B, and C until they became pregnant, 89 per cent of them would have conceived by following the formula. According to the observations in Table I, the largest number would have conceived during the first four months (Schedule A).

Comment

After comparison of the results of other methods with those of the formula for selecting the optimum time for conception, the conclusion is reached that, with the exception of the rat hyperemia test, which is the most precise for selecting the time of ovulation, there is no method at the present time that is as satisfactory. Although the number of cases upon which this report is based is admittedly small, the results would seem to substantiate the above statement.

The rat hyperemia test has revealed facts that are of value in the practical application of the formula. Ovulation occurs, generally, once every month, particularly in women at the optimum age for reproduction. The average fertile woman ovulates normally about 85 per cent of the time, or in 7 out of 8 cycles.[3] In the cases in which ovulation was studied for several consecutive months in the same individual, 93 per cent of the women showed a variation in the time of occurrence of ovulation of less than 3 days, while 80 per cent

exhibited a variation of less than 2 days. The fact that ovulation occurs on nearly the same day in consecutive cycles indicates the necessity of performing coitus on consecutive days.

It is advisable to practice one schedule for coitus or insemination for at least 4 cycles before the next schedule is used. During this first period of four months a woman with a fertility problem is likely to exhibit 2 out of 4 normal ovulation reactions. In the absence of a normal ovulation reaction, pregnancy is unlikely.

Summary

A method is described for selecting the optimum time for coitus or insemination for conception. The procedure is as follows:

1. Use 3 consecutive menstrual cycles to secure an adequate average of the length.

2. Inseminate or recommend coitus, following 5 days' abstinence, for 3 consecutive days beginning *2* days before the midcycle day.

3. If conception fails after following the above schedule for 4 months, inseminate or advise coitus, following 5 days' abstinence, for 3 consecutive days starting on the *third* day previous to the midcycle day.

4. If conception fails following the use of the two above schedules, inseminate or advise coitus daily, following 5 days' abstinence, for 3 consecutive days starting *1* day before the midcycle day.

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CYTOLOGIC DIAGNOSIS OF MALIGNANCY OF THE FEMALE GENERATIVE TRACT—A PATHOLOGIST'S VIEWPOINT

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MUCH has been written of late regarding cytologic studies in the diagnosis of malignant tumors of the female generative tract. These papers have presented the pros and cons of the value of the method, mostly favorable; some have hailed it with somewhat more than scientific enthusiasm.

Rarely, however, does one hear from the other half of the team, those who must do the work, the microscopists and screeners who labor behind the scenes to produce the statistics.

This paper is undertaken to present some thoughts and reflections gleaned from a fairly extensive personal experience and from innumerable informal conversations with fellow workers in this field.

One often hears the statement made that pathologists oppose cytologic diagnosis of cancer. There are, no doubt, some individuals who actually do oppose this method on personal grounds, but pathologists certainly do not, as a group, oppose any method which will permit earlier and more accurate diagnosis of malignant disease. They, of all persons, know the results of diagnoses made too late, and of too little or incompetent treatment. Until we can attack cancer from a different angle than at present, i.e., that of stamping out the fire before it has gained too much headway, our only hope lies in earlier and earlier diagnosis, coupled with increasingly efficient therapy.

Nevertheless, a number of pathologists do look upon cytodiagnosis with considerable coolness. Some of the reasons are given here:

A. Assumption of Responsibility on Scanty Evidence.—

It takes a considerable courage, on occasion, to commit oneself on the appearance of a few abnormal cells. Sometimes they are so obviously neoplastic that there can be no reasonable doubt. These are not the problem cases, however. We have all seen strange things happen to cells under the influence of inflammation and trauma and other unfavorable environmental circumstances. It is difficult, to say the least, to distinguish between true neoplasia and the changes which occur in cervical cells after exposure to radiation, for example. I have repeatedly seen experienced observers call a given slide positive, when the fact that the patient had received deep radiation therapy was deliberately withheld. All of us remember long hours spent poring over endless serial ribbons, searching for malignant changes which, when found, were present in only a few of the serial sections. With the knowledge that even with the best of tissue sections it is sometimes impossible to be certain regarding a diagnosis, is it any wonder that some of us are reluctant to commit ourselves on the evidence presented by a few scattered cells? Ex-

perience helps to erase a great deal of the uncertainty, but this experience is expensive to acquire, for literally thousands of slides must be studied before one is competent to express a reliable opinion.

B. The Defensive Attitude.—

Someone has said, "Everyone can make a mistake—except the pathologist." There are institutions in which the surgeon or the internist can make an error, even one costing the life of a patient, and the fact is overlooked or treated indulgently. But let the pathologist make a mistake and he will be assailed from all sides, regardless of the circumstances. Fortunately such situations are not as common as they used to be and are steadily becoming more rare, but they do exist still. One experienced pathologist recently said, "In my hospital a surgeon can open up a patient with coronary occlusion (with abdominal pain radiation), and if the patient dies no one says anything. But if I called a smear positive and it was not eventually confirmed, that same surgeon would be the first to attack me. I can't afford to undertake cytologic diagnoses. Their very nature makes for a considerable percentage of error, and I can't take the chance of being mistaken." This man is not being paranoid. He is forced onto the defensive by his fellow practitioners.

C. Work Load.—

Proper study of a cytologic slide requires much more time, on the average, than does that of a histologic section. Few can cover a smear thoroughly in less than 10 minutes. Most require 20 minutes, and in the questionable ones still more time will often be needed. This means that an average of 10 smears per day, not an unusual number even in a relatively small laboratory, requires about three and one-half hours of someone's time, nearly a half day. To the pathologist who must work alone, do all the autopsies, the frozen sections, the surgical tissues, the administration, and the frequent staff consultations which are perhaps the most important part of his job, a half day spent in such a manner is clearly impossible. He could review thirty biopsies, or more, in the same time, biopsies which would eventually have to be done anyhow, since few gynecologic surgeons indeed would undertake surgery on the findings obtained from a single cytologic slide. This is not the sort of work that can be delegated to residents or general technologists, as can many other duties, not unless they are especially trained and thoroughly experienced. The only answer lies in having enough trained "screeners" to handle the enormously time-consuming chore of eliminating the negatives.

D. Shortage of "Screeners."—

Trustworthy screening personnel are both scarce and expensive. Many small laboratories cannot afford a sufficient number to do the work properly. This is no job for interns and residents, though the latter can be trained, if they have any aptitude for microscopy and there is sufficient time; but they have other duties to perform, more pleasant ones for them usually, and, except for pathology residents, their time in the laboratory is limited. No sooner are they approaching completion of their training than they are transferred to another service. To send technologists to training centers is expensive business, and a very considerable number of those so trained are soon lost, due to marriage, or to personnel turnovers, and to the tendency to drift from job to job so common among technologists. Others discover they have no aptitude for this sort of work. Furthermore, only about 50 per cent of the trainees ever become competent.

It is the author's experience that screeners must be so constituted as to enjoy painstaking, tedious, and detailed work, or they will do a slipshod job. Even those who volunteer for screening admit that it is often boring, fatiguing work, and that the occasional periods of excitement attendant upon discovery

of a positive slide are more than offset by the infinitely more common and prolonged nonproductive periods. There are not many persons who can spend day after day on cytologic slides without eventually becoming much bored, and hence careless, or without actually developing such a hearty dislike for the whole business as to leave the field entirely.

Small wonder then that competent and conscientious screeners are difficult to find. Since the pathologist is responsible for the work of his helpers he must be sure that they are trustworthy. He must find them or abandon the project entirely, for it is no more reasonable to expect him to do all the cytological studies, even if he has the time, than it is to expect him to do all the urinalyses or blood counts.

E. Eye Fatigue.—

Should the laboratory director be fortunate enough to obtain a sufficient number of screeners to carry on a cytodiagnostic service, he must reckon with an imposing personal element—eye fatigue. There are technologists who can spend hours each day at a binocular microscope doing routine blood counts, where the cells are scarcely seen. Far different, however, is the reading of cytology slides, perhaps the most difficult sort of microscopy. Here the details within *each* cell must be observed. Screeners whose eyes have no refractive error may possibly be able to spend three hours per day at the microscope, in divided doses of 30 minutes each, provided no other microscopy is done. Rare, indeed, in our experience and in the experience of many others, are those who can spend more than one hour per day at screening without undue fatigue when other microscopic work must also be done. A tired screener is a careless one. Studying a slide covered with malignant cells induces no particular strain, since it is not necessary to spend so much time in looking. A negative slide, and particularly a doubtful one, should be studied by a screener who is fresh and alert, and who is free of personal telephonic and conversational interruptions.

One large laboratory, doing many cytologic examinations per day, employs a staff of five full-time screeners. These spend no more than three hours each per day in actual screening in divided doses, the rest being spent in duties not involving microscopy. Even so, a number of persons have developed enough eye strain to necessitate their leaving the field.

F. A Confirmatory Biopsy Must Be Done Anyhow. Why Not Do It in the First Place and Settle the Matter Once and for All?

This is a recurring question. Why bother with all the extra work and extra expense involved, when, should a positive slide be obtained, a biopsy will be done anyway, since few indeed would be so rash as to undertake radiation or surgical therapy without confirmation. Admittedly it is annoying to the pathologist to be required to process and study a tissue biopsy to determine whether or not his findings on a cytology slide were correct. A biopsy done in the first place would have perhaps settled the issue with a single procedure.

There are several viewpoints here. As desirable as it might be to do a cancer case-finding study on every woman past 35 years of age, thereby discovering a few cases of early cancer and perhaps saving a few lives, it is utterly impractical to do so because there are simply not enough trained personnel in all the world to maintain such a study. For every cytological slide which a pathologist could review, he could study perhaps 10 or 15 biopsy slides, but even routine case-finding biopsies would be impractical, from the economic standpoint if from no other, and there are other equally important considerations. Cytological studies are probably the most expensive ones made, from the laboratory standpoint, in time and in the need for especially

trained personnel. Actual biopsy, from the standpoint of the laboratory, is a much less expensive procedure, but there are insurmountable difficulties which makes its use as a screening procedure for routine use impossible. If then we must choose a screening method, let us choose the cytologic smear, but let us use it on selected patients, realizing its limitations and the technical difficulties attendant upon its use.

No pathologist of experience believes that actual biopsy will finally settle the issue in 100 per cent of the cases. He has seen too many exceptions to this, and if he has also had much experience in cytologic diagnosis, he has also seen instances in which the first biopsy, taken as a result of a positive smear, has failed to confirm the positive finding, confirmation coming later as a result of serial sections, repeated biopsies, or by the simple though undesirable method of letting nature take its course. Biopsy of the endocervix, the region in which one would expect most malignancies to develop and from which most positive smears are obtained, is difficult at best. Everyone has seen endocervical tumors missed on biopsy, only to be discovered later. There is as yet no satisfactory method of visualizing the intact endocervical canal, and without direct vision as a guide attempts at obtaining a representative biopsy are a hit-and-miss proposition. It is here, perhaps, that cytologic studies find their greatest field of usefulness, alerting those concerned to the possibility of a hidden lesion. Visible lesions are best biopsied directly, eliminating the intermediate step. Given proper supporting personnel, the cytodiagnostic smear is at least equally practical and probably more reliable than routine endocervical biopsy.

Summary and Conclusions

Pathologists working in the field do not doubt the value of cytodiagnosis as an adjunct to other methods of study. There can be no doubt that some otherwise unsuspected malignancies have been discovered and some lives have perhaps been saved. Many do doubt the universal practicality of this procedure; there are many other laboratory procedures in the same category which, in a University Hospital, backed up by a large teaching department and with ample personnel who are paid from funds of tax or endowment origin, are entirely practical, but which in the smaller independent laboratory cannot be done, regardless of how desirable they might be. Most pathologists work in small independent laboratories and most patients are served by them. Many of these men, being scientists in medicine, would rather not attempt the job at all than do it halfway. If your pathologist seems cool toward the idea of establishing a cytodiagnostic service, some of the facts presented above may have influenced his attitude, rather than any desire to avoid anything new, as has sometimes been charged.

807 BROADWAY

THE USE OF ETHINYL ESTRADIOL IN PREGNANCY*

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IN NORMAL pregnancy, the rate of estrogen and progesterone secretion reaches a peak at about the thirty-eighth week and rapidly declines from then until parturition.[1] The picture in late pregnancy toxemia and its associated accidents, therefore, may be considered one of premature decadence of placental secretion. A clearer understanding of the physiologic processes involved in the production of estrogen and progesterone has evolved from studies of estrogen metabolism in women. It has been deduced (1) that progesterone facilitates the metabolic conversion of the estrogens and hence depresses their rate of inactivation, (2) that estrogen inactivation products play an important role in the stimulation of sex steroid secretion, and (3) that the production of progesterone during the luteal phase of the menstrual cycle and around the thirty-eighth week of normal pregnancy is sufficient to reduce estrogen inactivation to such an extent as to remove the stimulus for sex steroid secretion.[1, 2] The regression of the corpus luteum in the ovarian cycle, and the reduction of the placental steroid hormones during the last weeks of normal pregnancy may readily be explained on this basis. It has accordingly been proposed[3] that the administration, during the middle months of pregnancy, of larger amounts of estrogenic material than could be metabolized by the available progesterone might supply a sufficient concentration of inactivation products to forestall any incipient premature deficiency of estrogen and progesterone.

It has been demonstrated that a progressive deficiency of the steroid hormones precedes the onset of late pregnancy toxemia, eclampsia, premature delivery, and intrauterine death.[1] It has been shown that a reciprocal relationship exists between the vascular supply to the placenta and the circulating level of steroid hormones, adequate vascularity being essential for the normal production and metabolism of estrogen and progesterone and adequate hormonal supply being equally essential for vascular development in the pregnant uterus. On this basis, it has never been felt that the primary abnormality responsible for late pregnancy complications was necessarily hormonal, but that this deficiency is always a contributory factor to the final syndrome which precipitates the clinical manifestations.[4] G. V. and O. W. Smith[5] state that stilbestrol causes an increased secretion of progesterone in human pregnancy (probably by the placental syncytium) through causing an increased utilization of chorionic gonadotrophin; and thus with a progressively increasing dosage obtained the clinical results:

*The ethinyl estradiol used in this study was kindly supplied by the Schering Corporation, Bloomfield, N. J.

A. Seventy-eight per cent of 219 women carried to 48 weeks, and 72 per cent obtained living children.

B. With 22 women, 83, 92 per cent, of their previous 91 pregnancies were complicated by one or another of late pregnancy complications, and only 31, or 35 per cent, resulted in living infants. On stilbestrol these 22 patients had an incidence of 64 per cent pregnancy complications and 16, or 73 per cent, obtained living infants.[3]

Material

This study comprises a group of 381 clinic patients. On arrival in the clinic at the hospital, alternate patients were chosen for treatment for the period from Jan. 1, 1948, to Dec. 31, 1948. They were given ethinyl estradiol 0.5 mg. three times a day from their first clinic visit until the day of delivery, from 2 days up to 7 months. In the treated group were 240 (63 per cent) primigravidas and 141 (37 per cent) multiparas.

There had been 72 previous abortions in the group studied, and in the pregnancy under study with ethinyl estradiol therapy only 5 abortions resulted, an incidence of 1.31 per cent: (1) 16-week abortion and on therapy 2 days; (2) 21-week abortion and on therapy 12 days; (3) 24-week abortion (patient with pyelonephritis) and on therapy 2½ months; (4) 26-week abortion and on therapy 11 days; (5) 24-week abortion and on therapy 2 months. It appears from this phase of study that a progressively increasing dosage schedule is not necessary for fetal salvage with patients who have had previous abortions.

There were 15 cases of toxemia in previous pregnancies and 28 cases (7.34 per cent) of toxemia in the pregnancies under study. Primigravidas comprised 21 (75 per cent) of the patients and multiparas 7 (25 per cent), with three of the latter having had toxemia during previous pregnancies. Statistics for the entire year of 1948 revealed an incidence of 7.27 per cent of toxemia among the clinic patients delivered at the hospital. Thus, it is apparent that such a standard dosage schedule as was used in this study did not decrease the chances for a pregnancy complicated by a toxemia.

In the series were 8 (2.08 per cent) cases of hypertension; 6 sets of twins of whom 2 sets were associated with toxemia; and one case of abdominal pregnancy which resulted in a stillbirth.

The side effects of the medication were relatively mild and resulted in: nausea, 7 cases (1.83 per cent); vomiting, 2 cases (0.52 per cent); skin manifestations, 4 cases (1.04 per cent). In only two of the cases were symptoms severe enough to cause the medication to be discontinued and then re-started a week later without any recurrence of symptoms.

During this same period the incidence of toxemia in 20 cases with a previous history of toxemia, in the private practice of one of the authors (C. H. B.), was 0.9 per cent. The dosage schedule used with these patients was a progressively increasing one: 0.5 mg. (1 tablet) three times a day for the first three months; four times a day during the fourth month; and gradually increasing the daily dose by one tablet every month until at term the patient took nine tablets daily, or 4.5 mg.

Also during the same period of this study 17 cases of pregnancy complicated by diabetes were observed by one of the authors (C. H. B.). These were treated with insulin and progressively increasing doses of ethinyl estradiol. In this group there were 15 vaginal deliveries of living full-term infants, all infants weighing less than 8 pounds. One cesarean section was done for an obstetrical indication (placenta previa). One patient had a macerated fetus at 7 months

of pregnancy, and this patient had insulin only. In a subsequent pregnancy, one year later, with insulin and ethinyl estradiol therapy, a living full-term infant was delivered vaginally.

From the study it also appeared that labor was approached, to a greater extent, with an effacing or effaced cervix; and labor was more rapid.

Summary

1. A standard dosage schedule of ethinyl estradiol, 0.5 mg. three times a day during pregnancy, will yield excellent fetal salvage with patients who have had previous abortions.

2. This standard dosage schedule of ethinyl estradiol did not materially reduce the incidence of toxemia of pregnancy.

3. A progressively increasing dosage schedule of ethinyl estradiol reduced the incidence of toxemia of pregnancy.

4. Labor was approached with an effacing or effaced cervix and labor appeared to be more rapid.

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PREGNANCY IN MYASTHENIA GRAVIS*

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MYASTHENIA gravis is a disease characterized by fatigability due to incomplete or distorted transmission of nerve impulses to the muscle across the synapse of the myoneural junction. There apparently is a disturbance of the acetylcholine-cholinesterase balance at the synapse. The pathological findings consist of small round cell infiltration of muscles, and in many cases the thymus persists to old age, with many lymphoid germinal centers. The cause is unknown, and no hereditary tendency has been shown. Distribution is about equal between the two sexes, with the highest incidence at adolescence or in the third decade. Since, during the last two trimesters of pregnancy, there may be a complete remission of symptoms, the disease must be affected by the pregnancy hormones.[1]

Prior to modern methods of treatment the disease was rapidly fatal, but now 80 per cent will survive. Neostigmine has been the drug of choice until very recently. The methylsulfate salt is given in doses of 0.5 mg. in 1:2,000 solution intramuscularly or intravenously. Atropine may be required to offset bradycardia, sweating, salivation, pallor, or collapse that follows the use of the drug. For oral therapy, neostigmine bromide is given in tablets of 15 mg., an average of ten tablets being required in twenty-four hours. Phosphate compounds recently have been introduced, the best because of its low toxicity being tetraethyl pyrophosphate. ACTH has been found to make the patients weaker. Thymectomy or radiation of the thymus has been beneficial.

Myasthenia gravis is very infrequently seen during pregnancy. Very little is written about this disease and pregnancy in the standard textbooks of obstetrics. Eastman[2] devotes a brief paragraph to the problem and makes the statement that it is a rare complication of pregnancy and the disease may be aggravated in pregnancy.

Viets, Schwab, and Brazier[3] reviewed the literature and found scant attention paid, with few cases reported. They added eight cases, all of which were treated with oral neostigmine. Most of their patients improved during pregnancy. Relapses frequently occurred late in the first trimester with remission during the last two trimesters. They cited an incidence of 1 in 63,268 between 1900 and 1940 at the Boston Lying-in Hospital. Since their report, several other cases have been reported which improved during pregnancy.[4, 5]

A few cases have been reported that were aggravated during pregnancy. Kennedy and Moersch[6] found in seven patients with twelve pregnancies that during five of the pregnancies the symptoms became more severe but in four cases there was improvement after either delivery or weaning. Wilson and Barr[7] also had a case that became worse during pregnancy and which was controlled by increasing doses of Prostigmine. Another such case was that of Harris and Schneider[8] whose patient was satisfactorily maintained on 90 mg.

*Presented at a meeting of the Los Angeles Obstetrical and Gynecological Society, Nov. 13, 1951.

of Prostigmine Bromide until she became pregnant. The dosage was progressively increased until in the seventh month she was getting 210 mg. daily plus several doses of the methylsulfate salt parenterally. Because of the downhill course she was delivered by cesarean section two weeks before term. Although the postpartum course was uneventful, she was taking from 325 to 400 mg. of Prostigmine orally per day one year after delivery.

Fortunately, the infants of mothers with myasthenia gravis infrequently develop the disease. McKeever[9] states that of ten known congenital cases, six were diagnosed in the neonatal period; and he added one case of his own, for a total of seven. The mother in his case ran a very bizarre course, with remission during the first five months, a relapse during the sixth month, another remission the day of delivery, followed by another relapse after delivery, and subsequent remission.

The following case is the first one reported of myasthenia gravis with a pregnancy complication which was treated with tetraethyl pyrophosphate. The mother was a 26-year-old white para iii, gravida iv. She developed myasthenia gravis at age 23, and was given the usual forms of treatment, including radiation of the thymus and neostigmine orally. Menstrual periods were regular, with 28-day interval, moderate flow lasting four or five days. Past medical and family histories were without significance.

Her first baby was a boy, weight eight pounds, four ounces, delivered by forceps, type unknown, after five days of labor. The second child, a girl of eight pounds, three ounces, was also delivered by forceps, after four days of labor. The third baby was a boy, seven pounds, eleven ounces, delivered spontaneously after one and one-half days of labor. From four to five months after each delivery there developed some type of pustular eruption of the fingers, followed by loss of the fingernails. The eruption lasted about a year in each instance. She had a similar dermatitis at age 11.

She was seen when three months pregnant at the request of Dr. Foley because of the amenorrhea. A diagnosis of early pregnancy was made. She felt better than before she became pregnant. Serology was negative; the Rh factor positive. Hemoglobin was 12.5 Gm., the red cell count 4.73 million, white and differential counts and urinalysis within normal limits. At the thirty-third week urinary-tract complications developed. Excretory urograms revealed bilateral hydronephrosis, Grade 3 to 4, with marked angulation of the right ureter and a moderate degree of hydroureter. There was also pyelonephritis that responded well to treatment. Twelve days before delivery she developed dysuria and loss of bladder control. There was pyuria as well. Response to mixed sulfonamide therapy was prompt. Delivery at term was uneventful. General anesthesia was used upon the recommendation of the internist and because of reluctance to use a spinal anesthetic in a patient suffering from a known neuromuscular disease. On the third postpartum day there was a mild relapse characterized by slight difficulty in swallowing. Increased tetraethyl pyrophosphate promptly controlled the situation.

Six weeks post partum she felt very well and her general condition was good. Medication dosage was back to the original maintenance dose of 3 to 4 minims of tetraethyl pyrophosphate three times a day with atropine sulfate in doses of from 1/75 to 1/150 grain with each dose of tetraethyl pyrophosphate, which are taken orally. Involution of the uterus was complete. There has been no evidence of myasthenia gravis in the baby. Three months after delivery the mother feels well and is maintained on the above doses of medication.

Summary and Comment

Myasthenia gravis is not a common disease, and when complicated by pregnancy it is quite rarely encountered.

In most of the reported cases the effect of pregnancy is favorable. If relapse occurs it happens more often at about the third month. Occasionally

both remission and relapse occur during the pregnancy. Labor, delivery, and the puerperium are usually uncomplicated. Rather paradoxically, labor frequently is rapid.

Another case is reported, the first known case complicated by pregnancy that was treated with tetraethyl pyrophosphate. Prior to the pregnancy the method of treatment was changed because of poor response to neostigmine. The patient felt better during pregnancy than at any other time, except for the short period when acute urinary complications developed. A brief relapse occurred on the third postpartum day that rapidly was controlled by a temporary increase in dosage.

The most satisfactory treatment at present seems to be with the phosphate compounds, the best of which is tetraethyl pyrophosphate. Atropine sulfate satisfactorily controls any side reactions of the drug. Radiation of the thymus frequently results in some improvement and there are advocates of surgical removal of the thymus.

The frequency of remissions during the last two trimesters suggests some relationship between the improvement and chorionic gonadotropin. Would it be justifiable to use chorionic gonadotropin as one of the adjuncts in the treatment of myasthenia gravis, particularly in women, even though the prolonged use of the hormone could possibly cause menstrual aberrations, or shall we be satisfied with the more physiological source of the hormone?

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"PIG FACE" FETUS, A TERATOLOGICAL STUDY

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FETAL monstrosities are neither uncommon nor unexpected in any large obstetrical service. However, the majority of the anatomical defects seen are essentially the same over the years. At the Bronx Hospital, we were fortunate in having the opportunity of seeing a monster which may be unique (Fig. 1). At the Carnegie Institute of Embryology no member of the staff had ever seen any such group of anomalies and a similar case could not be found in the literature. Dr. George W. Corner, Director of the Institute, found in Sir Jonathan Hutchinson's collection of medical pictures at the Welch Library of the Johns Hopkins Medical College a nineteenth century broadside of a "pig-faced lady" who seems to have represented a less extreme deformity than the case presented below. The uniqueness of the specimen, and the paucity of reports on the anatomical dissection of fetal anomalies prompted the authors to arrange for the teratological study of the fetus.

G. C., B.H. No. 222031, was admitted to the Bronx Hospital at 6:30 P.M. on Jan. 17, 1950. The patient was a 28-year-old primigravida whose expected date of delivery was Jan. 28, 1950. The patient had been observed by the Ryder Memorial Hospital of Puerto Rico, and an x-ray of the abdomen had been taken there on Nov. 12, 1949. The x-ray was reported as showing twins, one of which was six months in size and the other very small with overlapping cranial bones. On admission to the Bronx Hospital a flat plate of the abdomen showed a fetus, vertex presentation, near term, on the left, and on the right, in breech presentation, a much smaller fetus with a defective skull. The patient went into labor in the evening of Jan. 17, 1950, and the cervix was fully dilated at 9:00 A.M. on Jan. 18, 1950. Twin A was delivered with Kielland forceps applied to a vertex in left occiput transverse position and a living male infant in good condition, weighing 4 pounds, ½ ounce, was delivered. Vaginal examination now revealed a fetal monster to be present in the uterus. A difficult embryotomy was done with delivery of a 3-pound deadborn monster. The placenta was removed manually and the patient received 1,000 c.c. of whole blood during the procedure.

The mother had an uneventful puerperium and was discharged from the hospital on the ninth postpartum day. Twin A was also discharged from the hospital on the seventh postpartum day in good condition, weighing 5 pounds, 9 ounces.

Autopsy Report*

Gross Aspect.—The body measured 20.3 cm. from the crown of the head to the base of the spine. Approximately 1 cm. of this length was due to tissue thickening in the head area. The skin was very loose and wrinkled, due in part, apparently, to an edematous condition at delivery followed by subsequent fluid loss and fixation. A sparse amount of black hair was distributed over the posterior and lateral portions of the head. A definite neck was absent; the cervical tissue is bloated and flabby, and a shallow groove was the only

*This specimen was dissected by Mr. Barry Plunkett, student of Medicine, Johns Hopkins University.

separation between the head and the thorax. At the juncture of the head and body the skin was very thin or missing on the ventral aspect. The head was rather similar to that of a blowfish in appearance. A single, rounded proboscis-like protuberance occupied the region of the mouth and nose. Small, well-formed lips were recessed in the skin at the end of this puckered structure. No semblance of a nose was present. A small external auditory meatus was present on the left, and skin folds, suggestive of an immature pinna, were observable on this side also. Evidences of such structures on the right side were lacking. The right eye socket was covered by a membrane; the left socket was partially covered by such a membrane. No eyeball is visible. Diminutive eyelashes might be seen on both eyelids. No arms or arm buds were detectable. Body form in general was ill-defined. The legs were fairly well developed but gnarled and macerated, probably due to deterioration between the times of delivery and fixation. The left foot had three small toes and a great toe. The right foot had a long great toe and a very rudimentary fifth toe, with no intervening foot substance. A small penis was present about 1 cm. down on the left leg. About 1 cm. below this structure on the left leg was the anal opening which, however, admitted a probe to a depth of only 2 or 3 mm.

Fig. 1.—Specimen which has been resutured after embryotomy.

Skeletal System.—The ossification of the skeleton was in general retarded. It was, however, more advanced in the skull than in the remainder of the bones. Calcium deposits were heaviest in the supraorbital and mandibular regions (Fig. 2). The bony portions of

the inner ear also appeared well calcified. Centers of ossification were present in the vertebrae, but little bone formation was detectable. The spinal column failed to show the normal curves and in general was C-shaped, a single dorsally directed curve occurring at the level of T_7. The ribs, the normal twelve in number, were almost entirely cartilaginous. Because of the flexure of the entire body to the left the thoracic cage on that side was much compressed and deformed in comparison with that on the right side. The sternum was totally absent. The pectoral girdle was also entirely missing with the exception of the right clavicle, which was rather poorly formed. The left ala of the ilium was markedly less well developed than the right ala. The right femur was fractured at the juncture of its upper and middle thirds.

SKULL - LATERAL

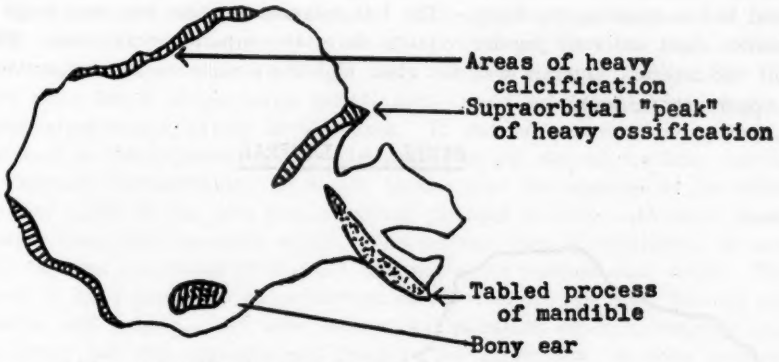
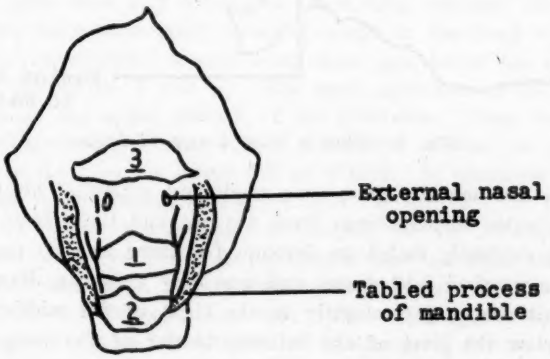


Fig. 2.—Sketch from x-ray of fetus.

SKULL - FRONTAL



1. Maxilla
2. Mandible
3. Single orbit

Fig. 3.—Sketch from x-ray of fetus.

Musculature.—The abdominal and pectoral muscles (with the exception of the muscles between the thorax and humerus, which were absent) were not unusual, but they were fused and poorly differentiated from each other. The muscles of the head and neck were less well developed and were infiltrated with much fatty tissue.

Thorax.—The diaphragm was fused to the lateral bases of the lung cages and extended from these points of attachment sharply upward, the center of the diaphragm being considerably above its expected position. It lacked anterior attachments, and the thorax and abdomen communicated freely. Just inside the pectoral cages and everywhere adherent to them were thick, white, mucoid adipose envelopes. The lungs were absent, as was the trachea. It would appear that the laryngotracheal ridge failed to differentiate, for all the elements formed from it were lacking (the larynx, trachea, bronchi, lungs, pleurae). The mucoid envelopes mentioned above were probably composed of degenerate mesenchymal tissue, the remnants of the splanchnic and somatic mesoderm from which the visceral and parietal pleurae would have developed, respectively. The heart was quite degenerate and mucocartilaginous, containing very little muscular tissue. Its weight was 2.19 grams. The walls were very thick. Distinct auricles and ventricles could not be discerned. The structure was quite rigid and would have been incapable of an effective pumping action. It was difficult to trace the major vessels, which were also atrophic. The superior and inferior vena cavae united before entering the heart. The left external jugular vein was large and joined with a smaller right external jugular vein to form the superior vena cava. The point of entrance of the internal jugulars was not clear and there were no subclavian vessels (there being no upper extremities).

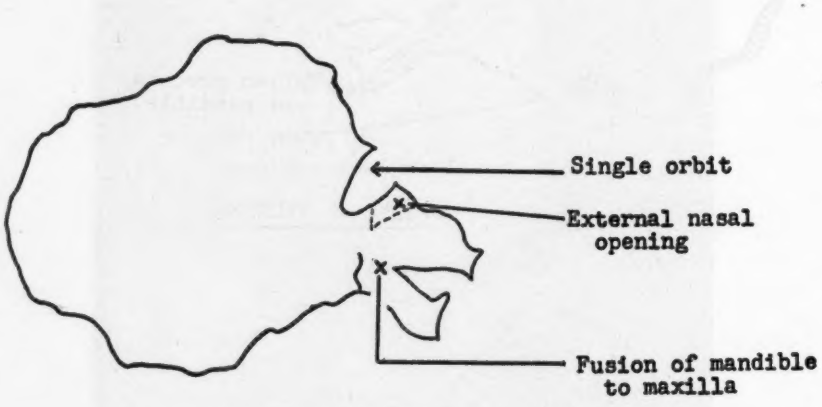


Fig. 4.—Sketch from x-ray of fetus.

Abdomen.—The abdominal organs were small and somewhat altered from their normal positions. The pancreatic outpocketings from the gut and the splenic primordium from the dorsal mesogastrium evidently failed to develop, for there was no trace of either pancreas or spleen. The liver weighed 2.10 grams and was only 2 cm. in diameter (maximum). It was located retroperitoneally, just slightly to the right of the midline. About one-half of its substance lay below the level of the inferior border of the lung cage. The intestines were quite firm and very short, showing some kinking. The mesentery was extremely thin. The intestine ended blindly cephalad. The blind end rested against the right pectoral cage at the level of the sixth rib and passed caudally over the center of the liver. There was no stomach. The absence of the abdominal organs mentioned may be explained by failure of development of that portion of the gut from which these organs usually arise. The kidneys were in their normal positions and are well shaped, but they were quite small. The right kidney weighed 95 mg.; the left kidney weighed 45 mg. The adrenals were also well formed but singularly atrophic. The right adrenal had the typical three-cornered-hat shape and weighed 20 mg. The left adrenal weighed 15 mg. Inferior to the kidneys at the upper limits of the rectum were the two testes in the process of descent.

Brain.—The meninges were quite thick and very strongly adherent to the skull, which was of eggshell consistency except along the suture lines. The tentorium cerebelli between the cerebellum and cerebrum was well developed. The brain completely filled the cranial cavity. The cerebellum was rather large, being approximately one-half the size of the cerebrum. The cerebrum was not divided into left and right hemispheres but consisted of a single lobe, and the sulci and gyri were minimal. The anterior inferior part of the cerebrum was a mere pedunculated appendage due to the abnormal form of the skull and the more accelerated growth of the brain than of the skull. (The unusual shape of the skull can be seen from the lateral and anteroposterior views of Figs. 2 and 3.)

Head.—Since the head of this fetus was the focal point of interest, discussion of it has been reserved till last. To present it as a unit, repetition of some previously mentioned facts may be necessary.

The thymus and thyroid were not unusual. The esophagus ended blindly distally at the juncture of the head and thorax. It was quite dilated in comparison with the remainder of the gastrointestinal tract. The salivary glands were not macroscopically distinguishable because of the edematous state of the tissues. Although the face showed two eye openings on inspection, dissection revealed no bony structures between them but only a thin band of connective tissue, there being thus a single bony orbit in actuality (Fig. 3). There were no definitive bulbi but a single large retinal area in an advanced stage of degeneration. Heavy pigmentation was apparent in this area. It was obvious that the visual apparatus did reach a stage of development comparable to that of the rest of the body but had undergone more extensive degeneration. It would appear that the absence of the external nose and the peculiar shape of the jaws had permitted the eyes to come into much closer relation with each other than they normally would. The retinas actually overlapped to some degree although the external apparatus (lids, etc.) had not quite reached that stage. The internal ears appeared to have developed in proportion to the rest of the head, but no middle ears were detectable and only the left side showed an immature external auditory meatus and pinna. The lower jaw was immobile and fused to the upper jaw. A bony process extended from the anterior inferior portion of the mandible on each side to a point just lateroinferior to the ocular opening bilaterally (Figs. 2 and 3). Both the mandible and maxillae were narrow and semicircular in frontal view. Together they formed the long proboscis-like affair mentioned previously. As stated before there was no evidence of an external nose, and nowhere did the skin show any structures resembling external nares in any stage of development. However, there were small nasal openings in the bony structure of the face. The nose and nasopharynx occupied a very small area just below the eyes in the proximal portion of the upper jaw (Figs. 3 and 4). The nasal apertures in the maxilla opened just beneath the orbit high on the upper portion of the proboscis. There was no differentiation of nasal bones, the entire structure being simply a chamber recessed in the elongated maxilla with openings much like those on the upper bill of a bird. It appeared that the mandibular and maxillary processes in elongating interfered with the development of the nose. Fusion of the median nasal and maxillary processes was effected, but the subsequent medial compression of the median nasal processes failed to materialize and the nasal chamber became incorporated in the proximal maxilla in a very rudimentary form.

We are indebted to the Carnegie Institute of Embryology, George W. Corner, M.D., Director, for their great interest and invaluable aid in arranging for the anatomical dissection of the fetus.

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COMPOSITE ENDOMETRIAL CARCINOSARCOMA, LEIOMYOFIBROMA, AND INFILTRATING CERVICAL EPIDERMOID CARCINOMA IN THE SAME UTERUS

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THE composite endometrial carcinosarcoma of the uterine fundus is a rare neoplasm, but such a tumor associated in the same organ with an unrelated leiomyofibroma and an infiltrating cervical epidermoid carcinoma is a phenomenon worthy of reporting.

N. D. R., a 64-year-old woman, native of the Philippines, observed slight vaginal bleeding occurring continuously since Aug. 15, 1950, and persisting for a three-week period. At that time a diagnostic curettage was performed; the biopsy revealed endometrial adenocarcinoma.

The patient had otherwise been in very good health except for slight hypertension and diabetes mellitus which did not require insulin. She had given birth to five children without gynecologic complications. One daughter had a radical mastectomy for cancer of the breast performed by one of us (G. T. P.) ten years ago with no evidence of recurrence in the interval.

On physical examination she was a pale, 64-year-old woman with a blood pressure of 184/88 and had not sustained any loss of weight. Except for evidences of hypertension and arteriosclerosis, the positive findings were limited to the internal genitals. The uterus was about twice the normal size but was freely movable without evidence of fixation and with no parametrial induration. The cervix was slightly scarred but otherwise normal.

Operative Procedure.—The patient was admitted to the Doctors Hospital, where, on Sept. 24, 1950, a radical panhysterectomy was performed. There was no evidence of metastasis within the abdomen. The liver was normal. There were no enlarged iliac, obturator, or periaortic lymph nodes. The rectum and bladder were free of invasion. The surface of the uterus was smooth. The uterus, the broad ligaments, the cervix, and a liberal cuff of the vagina were removed with the specimen.

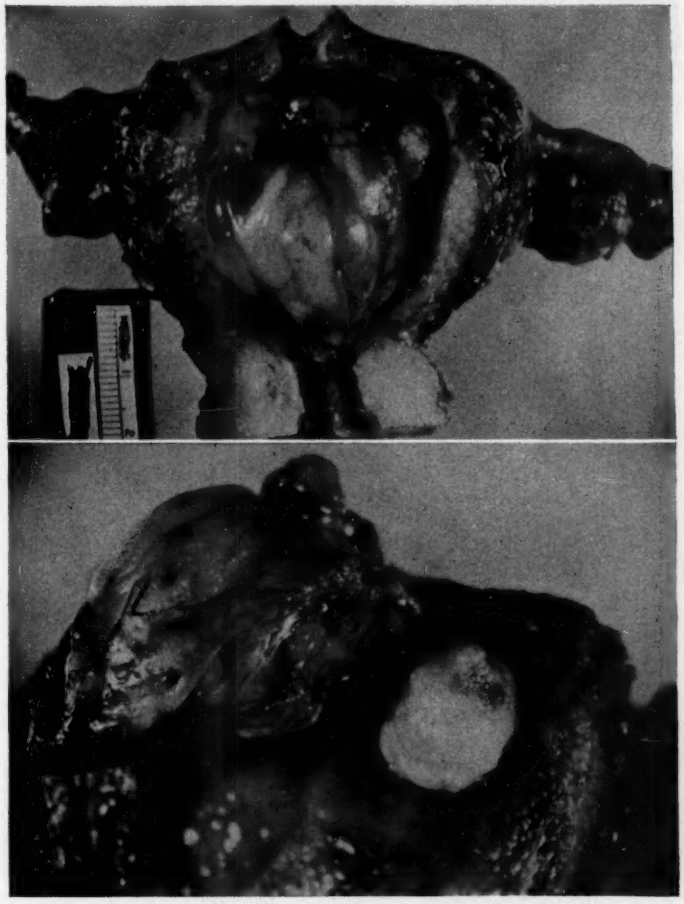
In the third postoperative week a prophylactic radium vaginal bomb was inserted for a dose of 1,250 mc. hr. against the vaginal fornices. She convalesced without complication.

Examination of Gross Specimen.—The specimen was the uterus with both adnexa. The uterus measured 10.5 cm. in greatest length, 6.5 cm. in greatest width, and 5.0 cm. in greatest anteroposterior diameter. The portio had a mildly injected surface and a vaginal cuff. The cervical canal was 1.8 cm. long, the rugae were slightly distorted, and a pedunculated polyp 4 by 2 by 1 mm. arose from the anterior wall. From the midfundus arose a pyriform yellow-white mass, 5.3 by 2 cm. The tip was ragged and hemorrhagic. The surface was intermittently nodular and smooth. The cut surface was homogeneous, fish-fleshed, and relatively soft. The base was sharply defined from the myometrium to which it was attached. Between its left side and the left horn was an hour-glass shaped fibroid 2.4 by 1.8 by 1.4 cm., half buried in the myometrium, half projecting into the uterine cavity. The submucosal half compressed the pyriform mass. Its mucosal surface was smooth. The rest of the endometrium was thin, pink gray, and had numerous pin-point clear cysts. The myometrium measured 1.0 to 1.3 cm. in thickness, was firm and had prominent vessels. The serosa was smooth. The right ovary was 1.9 by 1.7 by 1.0 cm. and had many small clear cysts. The tube measured 5.7 cm. in length. The serosa had several small cysts. The left ovary measured 2.3 by 1.5 by 0.8 cm., had a nodular surface and a few small clear cysts. The tube was 5.5 cm. long.

Microscopic Study.—The pyriform mass was endometrial in nature, the glands and stroma intermingled in variable proportion in different areas. The glands were lined chiefly by carcinoma cells, tall, opaque, macronucleated, hyperchromatic, and rich in bizarre mitoses.

Some were single layered, some papillated, some solid nests. The papillated glands were concentrated and closely packed at the tip, which shows the result of the curettage. Toward the base, the carcinomatous glands were associated with dilated glands lined by noncancerous epithelium varying from very flat to tall and hyperplastic. The majority of the stromal cells were malignant and many were giant in size. Macronucleation and hyperchromatism were marked, mitoses were abundant and bizarre. There was local penetration into the myometrium. Toward the base, particularly on the side compressed by the fibroid, glands were very scanty. Likewise at the base, small areas had normal glands and a very fibrous stroma. The endometrium over the fibroid was atrophic, had a few cystically dilated glands and small surface nonmalignant papillomas. The endometrium in the rest of the uterine cavity was thin, had a few cystically dilated glands, and focal marked epithelial hyperplasia. The myometrium appeared normal. The arteries had intense arteriosclerosis, frequently progressing to complete fibrous occlusion. These changes were more severe near the masses than in other parts of the uterus.

A.



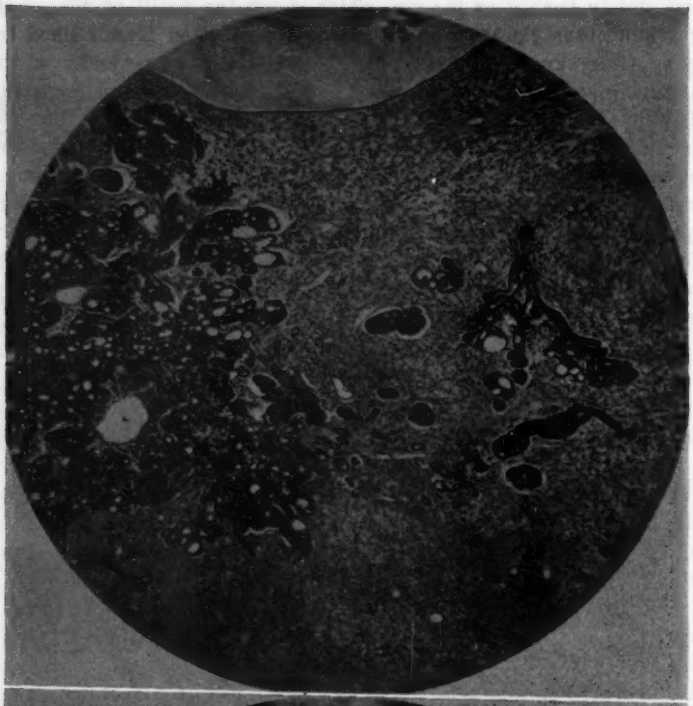
B.

Fig. 1.—*A,* The large polypoid tumor fills the uterine cavity and the tip presents at the internal os. A partially hidden leiomyofibroma is visible in the left horn.

B, Another view of the tumor mass showing the base arising from the fundus of the uterus and the pressure effect of the adjacent submucosal fibromyoma.

On the portio vaginalis of the cervix to the internal cervical os, the normal epithelium was replaced by malignant squamous epithelial cells mainly of spindle type. Near the external os, there were a few small pearls and nests of Pagetoid cells. At the internal os,

Fig. 2.



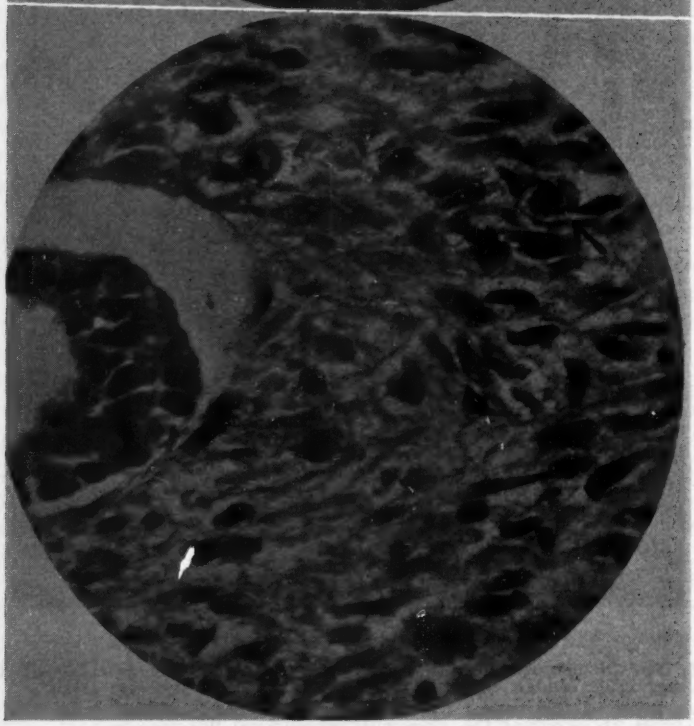


Fig. 3.

Fig. 2.—The tip of the mass shows both the glandular adenocarcinomatous element and the bizarre cellular stroma. (×45.)

Fig. 3.—The higher magnification showing the glands lined by neoplastic cells having anisocytosis, macronucleation, hyperchromatism, and loss of polarity. The stromal cells display the same malignant characteristics. There is one bizarre mitosis in the microscopic field (arrow). (×400.)

some of the glands were only partially lined by cancer cells. The veins and lymphatics in the lower cervix were widely invaded. A rim of normal squamous epithelium covered the edge of the vaginal cuff. The arteries were moderately sclerotic. The ovaries had several small inclusion cysts containing material varying from amorphous to partially calcified mucus. The tubes showed senile fibrosis and small serosal cysts.

Pathological Diagnosis.—(1) Primary endometrial carcinosarcoma, (2) postmenopausal endometrium, (3) fibromyoma of uterus, (4) primary squamous-cell carcinoma of cervix, (5) inclusion cysts of ovaries, (6) serosal cysts of tubes.

Carcinosarcoma of the Uterus

One of the rare curiosities of gynecologic pathology is the so-called carcinosarcoma of the uterus. This malignant mixed-cell tumor of the uterus has the peculiar feature, in common with Wilm's embryonal adenosarcoma of the kidney and sarcoma botyroides of the vagina, of possessing both carcinomatous and sarcomatous elements in its epithelial and stromal structure. The tumor is almost invariably polypoid and in the majority of cases originates from the midline of the fundus or posterior wall; this last fact has influenced some observers to consider the likehood that it is a developmental anomaly associated with Müllerian duct fusion. In this theory, the genesis is in cell rests resulting from the fusion of the paramesonephric ducts. The polypoid neoplasm may be small or gross, but it is characteristically intraluminal.

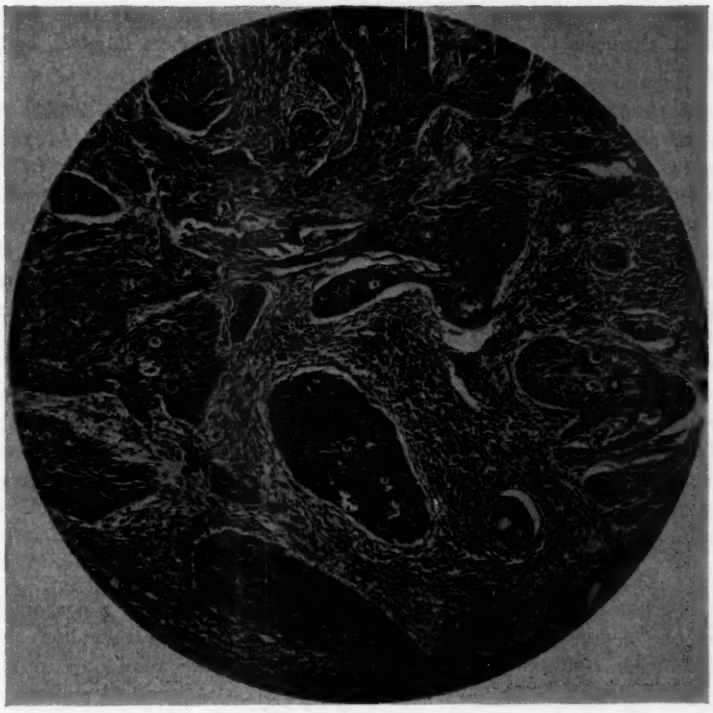


Fig. 4.—The neoplasm of the uterine cervix. The nests of epidermoid carcinomatous cells are chiefly spindle in shape but some show pearl formation and transitions from one type to the other.

Only 2 to 3 per cent of malignant tumors of the uterus are sarcomas; most of these neoplasms are leiomyosarcomas associated with or independent of leiomyomas of the uterus. It is impossible to compute the relative incidence of carcinosarcomas of the uterus, but admittedly it is one of the extremely rare malignant neoplasms. Many of the tumors reported in medical literature as carcinosarcomas will not bear critical review, because some anaplastic carcinomas show marked polymorphism of cells, which resemble sarcoma, e.g., the spindle-cell metaplasia found in carcinomas of the thyroid, esophagus, x-ray cancers of

the skin, and occasionally in endometrial cancers occurring in uteri which have been subjected to previous intracavitary radium application. In one of our patients, a large intracavitary carcinosarcoma of the uterus was found associated with an independent discrete leiomyofibroma and an endocervical epidermoid carcinoma (Fig. 1, *A* and *B*).

No pathognomonic diagnostic features permit a preoperative appraisal of the character of the tumor. The inconstant uterine bleeding (menorrhagia and metrorrhagia) follows no consistent pattern and may be less persistent and profuse than obtains in the cases of the common endometrial cancer. The average age of the patients with endometrial carcinosarcoma falls in the decade of 55 to 65 years.

The polypoid tumor is soft grayish pink and sessile. The surface may be ulcerated or intact. Foci of hemorrhage may be seen on cut surface of the lesion. The sarcomatous component with its scarf of endometrial cancer is truly different in microscopical character from the sarcomas occurring in fibromyomas; it is an endometrial stromal sarcoma. Lisa and associates have asserted that the mesenchymal portion of the tumor, i.e., the connective tissue portion, may elaborate intercellular material such as collagen, cartilage, and bone, which confirms the mesenchymal genesis of the sarcomatous part. Moreover, in the reported cases reviewed by Saphir and Vass, none of the metastases exhibited the combined mixed tumor, that is to say, the metastases were either carcinomatous or sarcomatous. If the metastatic foci were both sarcomatous and carcinomatous, the identity of the primary neoplasm would be assured, but this phenomenon seldom occurs, therefore it may be assumed that the composite elements of the tumor are capable of behaving in a dissimilar manner.

The intriguing mode of origin of this tumor has puzzled many pathologists, who have suggested several theories (Virchow, Ewing, Herkheimer, Robert Meyer, Jaffe). Meyer's three groups are:

1. *Collision tumor,* in which a primarily independent carcinoma and a sarcoma arise at different sites and fuse by contiguity of growth. Ewing thought of these tumors as mutually invasive.

2. *Combination tumor,* in which the two malignant blastomatous elements are derived from one stem cell as in the Wilms adenosarcoma of the kidney.

3. *Composition tumor,* in which the parenchyma and stroma of the single tumor have become neoplastic together (true carcinosarcoma). Ewing admitted that a common irritant or incitor could simultaneously produce neoplasia of both the epithelial and connective tissue elements. It is conceivable that either the carcinoma or sarcoma could precede, follow, or be coincidental with the other. Virchow, who labelled the tumor as carcinosarcoma, believed that, within the primary carcinomatous or sarcomatous elements, the stromal or epithelial fractions, respectively, were subsequently or simultaneously stimulated to malignant growth. Herxheimer, who preferred the term carcinoma sarcomatodes, held the occurrence to be more frequent in primary carcinomas, in which the carcinoma stimulates an excessive stromal overgrowth to the point wherein the proliferation becomes sarcomatous.

Summary

A report is presented of a composite carcinosarcoma, formed of a conjoined endometrial adenocarcinoma and endometrial sarcoma and developing as an intracavitary mass from the midline of the uterine fundus. Within the same uterus were found an unrelated and apparently coincidental benign leiomyofibroma and an infiltrating cervical epidermoid carcinoma.

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RUPTURE OF A SUBSEROUS VEIN ON THE SURFACE OF A UTERINE MYOMA CAUSING MASSIVE INTRAPERITONEAL HEMORRHAGE

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THERE have been fifty-five cases of spontaneous rupture of a subserous vein of a uterine fibroid causing massive intraperitoneal hemorrhage reported in literature. The condition was first mentioned by von Rokitansky[1] in his textbook in 1861. Ransohoff and Dreyfoos,[2] in 1921, reported nineteen cases and described two of their own. Shapira and Starr[3] reported two cases in 1932. In the recent literature, Schneider and Jemerin[4] reported one case in 1942 and Woodruff[5] reported a case in 1948. Hamilton[6] and Shelfo[7] have also reported cases.

Varices of leiomyoma have been attributed to congestive changes resulting from torsion of the tumor mass and pressure of irregularly growing leiomyomas. These varices are subserous, between the tumor capsule and the peritoneum. The causes of rupture appear to be direct trauma to the abdomen, sudden exertion or straining, erosion of the vessel from friction, or pressure of the tumor against the sacral promontory. It may also tend to occur more frequently when there is increased dilatation during menstruation and parturition. Inflammation of the tumor and torsion of the tumor pedicle have appeared to play a role in rupture of such a varix.

Case Report.—Mrs. I. D. (512132), a 37-year-old, married, Negro woman, was admitted as an emergency to the Detroit Receiving Hospital on Feb. 12, 1951, complaining of sudden onset of generalized abdominal pain, weakness, and syncope while riding in a bus. Her last mensis had occurred at the end of January and was normal. The previous menstrual period had been in December. Her only pregnancy resulted in a miscarriage in 1943. She stated that her abdomen had been protuberant for some time, and that she had had a known myomatous enlargement of the uterus for several years.

Physical Examination.—Her blood pressure on admission was 60/30, pulse 110, respirations 30, and temperature 96° F. Examination revealed an obese Negro woman in obvious shock. The chest was clear and the heart normal.

The abdomen was protuberant, distended, and diffusely and slightly tender without evidence of marked peritoneal irritation. Very slight tympanites was present. Pelvic examination revealed a large, multinodular uterus which filled the lower abdomen. The cul-de-sac was not tender, and there was no cellulitis nor fixation. Left lateral abdominal wall and cul-de-sac aspiration tappings with needle and syringe did not permit withdrawal of any blood. Extremities were cool and moist.

Preoperative Impression.—Despite failure to obtain a positive intraperitoneal "tap" for blood, she was believed to have an intra-abdominal hemorrhage, based upon the evidence of occult hemorrhage and the nontympanitic, abdominal distention with slight and diffuse abdominal tenderness as well as a somewhat "doughy" feel of the abdomen. Considered causes were ruptured tubal pregnancy or torsion of an ovary or of a pedunculated myoma with rupture of a vessel. Other conditions considered (not necessarily involving intra-abdominal hemorrhage) were: volvulus, intussusception, mesenteric thrombosis, pancreatitis, or ruptured gastric ulcer.

Treatment.—The patient received three 500 c.c. transfusions of blood, and an exploratory laparotomy was done. On entering the peritoneum, approximately 1,500 c.c. of blood and clots were found in the peritoneal cavity. A myoma, extending above the umbilicus, was present and there was, on the anterior surface of the myoma, a large varix 1.5 cm. in diameter which had ruptured and was bleeding (Fig. 1). The bleeding point was clamped and sutured and since the patient's condition was fairly good, a subtotal hysterectomy was done. The immediate postoperative condition was satisfactory and the postoperative course was uneventful.

Fig. 1.—Large pedunculated myoma of the uterus measuring 16.5 cm. in greatest diameter. Bleeding point (denoted by arrow) was from a rupture of the large varicose vein pictured above.

Comment.—The case herein presented is similar to those described in the literature. The rupture of the vein was spontaneous, there being no history of trauma or sudden exertion and straining. The differential diagnosis was not aided by the negative lateral abdominal wall and cul-de-sac taps, and our failure to aspirate blood was undoubtedly due to faulty technique in performing the puncture.

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A TABLE FOR GYNECOGRAPHY

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(From the Michael Reese Hospital)

IN 1929, we reported a new type of radiographic table which was suitable for pelvic pneumograms.[1] This table served with satisfaction for many years but it lacked certain flexibilities and refinements. It was a single-purpose unit which could not be used satisfactorily for other types of radiographic procedures. Over a period of more than twenty years, thousands of pneumographic examinations were made but the total number per day was small. Since the equipment for this procedure could serve no other purpose, the radiographic room containing the unit stood idle a large part of the day. In order to utilize our desperately crowded department to better advantage, we conceived the idea of using the room both for urography and gynecography. To do so, we found it necessary to use two separate tables, one of which had to be kept in a storeroom. The tables were interchanged when necessary, thus necessitating a duplication of effort. What we required was a multipurpose table suitable for gynecography, urography, and other types of radiographic examination. For the purpose of obtaining satisfactory pneumograms, a modified knee-chest position with the patient's head and chest lower than the pelvis, is essential for maximum pelvic visualization and minimum distortion. The Sisk urological table was particularly well adapted to fulfill our needs with minor modifications. It required only the addition of an adjustable leaf on the end of the table to give us the necessary facility for the proper positioning of the patient.

We are well aware of the fact that gynecography may be performed with the use of the regular radiographic tilt table when the anatomic framework of the patient lends itself to a reasonable approximation of the position necessary to obtain adequate roentgenograms. At best, this is possible only in a very small percentage of patients. In previous publications,[2-3] the authors have stressed the best position and its value for obtaining diagnostic gynecographic films. Over a period of more than two decades numerous inquiries have come to us concerning the technique of this procedure, and, invariably, the inability to obtain the necessary apparatus has been commented upon. It was our thought that, with the development of a suitable table, there would be a more widespread interest in this special diagnostic method which we have come to regard as an exceedingly accurate diagnostic procedure.

In the hands of an expert gynecologist, bimanual examination is a reasonably adequate method of diagnosis. However, we must recognize the limitations of both rectal and vaginal examinations and the diagnostic errors which occur even in the hands of experts. These errors are revealed all too often at laparotomy. We are all cognizant of the limitations which exist due to obesity, rigidity of patients, fixation of the pelvic organs, pain and tenderness within the pelvis, the necessity for rectal examination in virgins, the extent of pathology which may be present, fixed retroposition of the pelvic organs, etc.—all of which may render bimanual examination subject to conflicting interpretation by successive examiners. This is only a partial list of the conditions in which marked differences of opinion may occur. Only under the most favorable conditions can one rely on physical findings alone for diagnosis. On the other hand, with the aid of pneumograms, one may clearly demonstrate specific pathologic lesions on the film, providing such lesions are limited to the true pelvis. In addition, the normal genital status may be demonstrated in some instances where symptomatology is

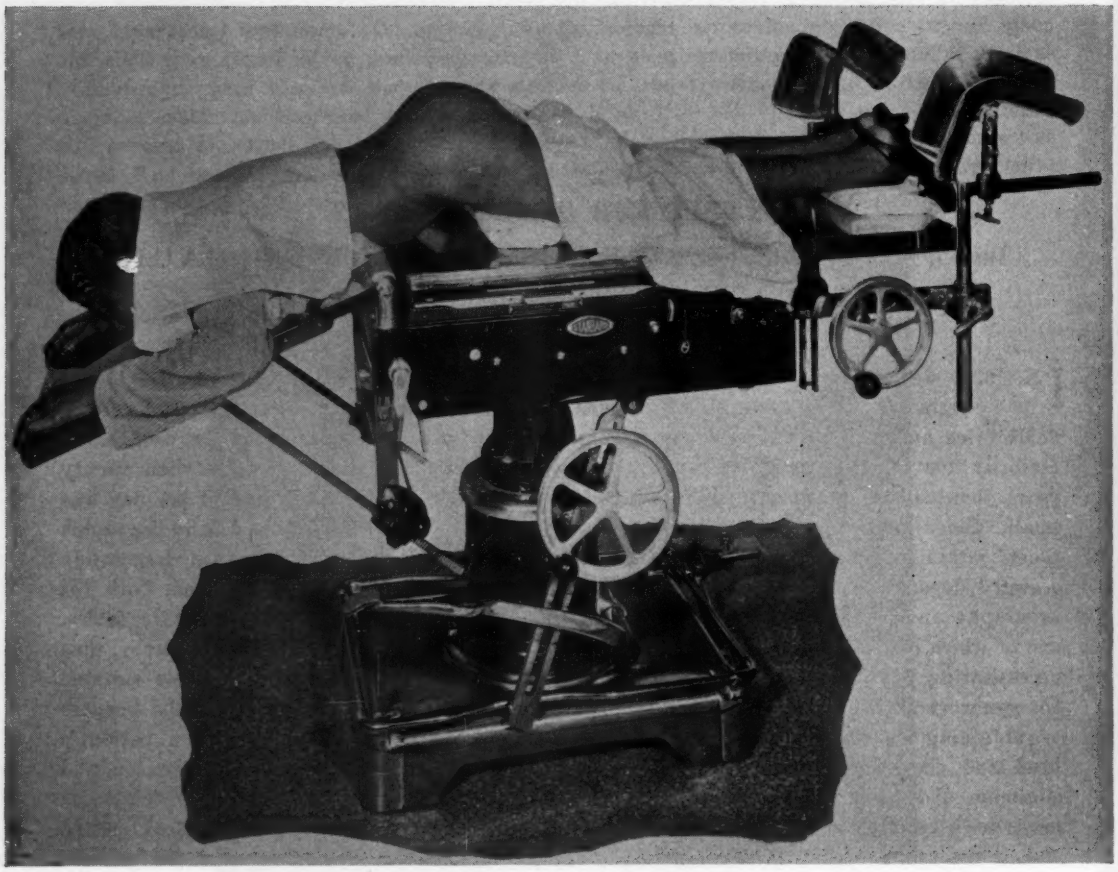

Fig. 1.—Authors' modification of Sisk urographic table with patient in best position for pneumoroentgenography and complete gynecography.

obscure and physical findings indefinite, thus obviating exploratory laparotomy.[5, 6] The method has proved valuable also in certain instances where it is necessary to determine whether female pelvic organs are present as in the case of pseudohermaphroditism in young individuals where sex was undetermined previously. Hypoplasia and pelvic anomalies of all varieties are clearly recognizable by this technique, thus making it unnecessary to resort to surgical exploration. Pneumograms serve as a permanent record of the pelvic status, whether normal or abnormal, and may be viewed by various physicians whom the patient may wish to consult. They also serve as a basis of comparison in the light of the changing pelvic status in the course of time.

The chest physician of today relies on radiological diagnosis of pulmonary disease to a marked degree. The gynecologist should, in our opinion, similarly avail himself of the advantages of roentgenograms after pneumoperitoneum.

Since developing this new table, we find it has served the needs of both the Departments of Urology and Gynecology satisfactorily, and it has been used also for general radiology. The equipment is so arranged that, with the movable leaf attached, it serves for gynecography, and when the leaf is removed, the table is left as it was originally designed for genitourinary roentgenography.

The illustrations herewith (Figs. 1 and 2) give a rather complete idea regarding the modified table with the requirements for gynecography.

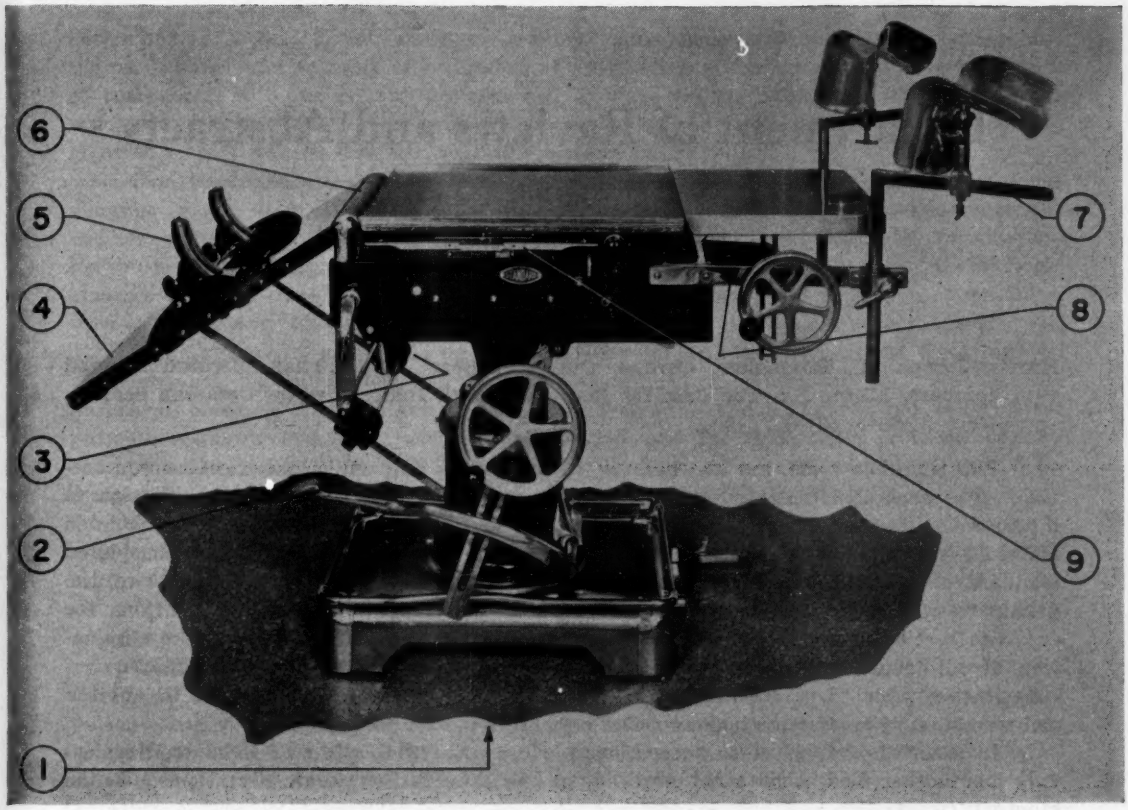

Fig. 2.—Detail of authors' new table for gynecography.

1. Sisk genitourinary table.
2. Lever for hydraulic lift.
3. Self-retaining hand crank to raise and lower adjustable leaf.
4. Special drop leaf for positioning of patient. This can be easily removed and the table used for genitourinary procedures as per original design. The attachment is so designed that it is automatically self-locking without the use of clamps, etc.
5. Special shoulder rest, adjustable.
6. Rubber roller to prevent bruising of skin over sharp table edge.
7. Elongated stirrup bars to give greater flexibility.
8. Extended supports for stirrup bars for better positioning of patient for bimanual examination and for transuterine instillation of gas and opaque media.
9. Bucky grid.

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Department of Reviews and Abstracts

Selected Abstracts

Cesarean Section

Harris, Joseph M., Rosenblum, Gordon, Ginsburg, Bearl L., Stollman, Bernard D., and Fenmore, Milton S.: The Case for Reevaluation of Indications for Cesarean Section, West. J. Surg. **59**: 337, 1951.

The time has come, say the authors, to re-evaluate the indications for cesarean section. The general attempt of obstetricians to limit the incidence of cesarean section to 6 per cent or less has resulted in a persistent high mortality for the fetus and an avoidable maternal trauma. Midforceps operations, which until recently have been considered standard obstetrical procedures, should be eliminated. The routine management of the primipara with breech presentation by cesarean section is advocated. Indications for cesarean section should be liberalized and extended, the ultimate goal being the elimination of all traumatic vaginal deliveries. The discriminatory regulation which requires consultation prior to performing any cesarean section appears to the authors ill advised and tends toward procrastination and makes cesarean section a unique operation.

In a series of 2,070 cesarean sections performed at the Cedars of Lebanon Hospital only one mother died, a maternal mortality of less than 0.05 per cent. One thousand nine hundred twenty-one consecutive cesarean sections were performed without a maternal death. Fetal mortality during a 13-year period from 1937 to 1950 was 3.13 per cent for vaginal deliveries as compared to 2.99 per cent for cesarean sections. There was a maternal morbidity of 14.04 per cent in the last series of 2,070 cesarean sections. In this report the most common indication for operation was cephalopelvic disproportion which made up approximately one-half of the indications for operation. Previous cesarean section is always an indication for a repeat operation in subsequent pregnancies. Uterine bleeding of placental origin made up approximately 10 per cent and fetal indications provided about 5 per cent of the indications for operation. It is felt that cerebral trauma to babies producing delayed sequelae such as spastic paralysis and mentally defective individuals can be in large part avoided by liberalizing the indications for the cesarean operation.

This paper created much discussion at the Pacific Coast Obstetrical and Gynecological meeting at which it was read. Many and varied were the opinions expressed. The discussion ranged all the way from serious criticism and conscientious objection to the suggestion that perhaps some day all women might be delivered by cesarean section. However, the discussers seemed to agree that the time has come for the elimination, in so far as it is possible, of the traumatic vaginal delivery. Cesarean section is to be preferred to any operation other than the simplest type of low forceps delivery.

WILLIAM BICKERS

Endocrinology

Greenblatt, Robert B., Barfield, W. E., Garner, Calk, and Harrod, J. P., Jr.: Evaluation of an Estrogen, Androgen, Estrogen-Androgen Combination, and a Placebo in the Treatment of the Menopause, J. Clin. Endocrinol. **10**: 1547, 1950.

Four tablets identical in appearance were prepared, one a placebo, one containing 0.25 mg. of diethylstilbestrol, another containing 0.25 mg. of diethylstilbestrol and 5 mg. of

methyltestosterone, and still another containing 5 mg. of testosterone. The tablets were designated as A E-1,2,3, and 4 and the contents were unknown to both the physicians and the patients in order to avoid any influence of pre-existing prejudice in evaluating the results of treatment. A course of therapy consisted of three tablets a day for thirty days after which time the medication was switched to another of the preparations either immediately or after a short wait so that the original symptoms might return.

One hundred two patients, both private and clinic, with menopausal symptoms, ranging in age from 23 to 62 years, the average being 44 years, were exposed to 284 courses of therapy. Subjective changes such as "hot flushes," insomnia, formication, nervousness, and changes in libido; and further objective factors revealing vaginal cytologic changes, vaginal bleeding, breast turgidity, pelvic congestion, and acne were the criteria used in evaluating the result of the four different types of therapy.

When stilbestrol alone was being taken, 96.9 per cent of the patients were relieved of menopausal symptoms but 30.5 per cent complained of nausea and 34.2 per cent experienced bleeding from an intact uterus. Eighty-nine and six-tenths per cent of the patients receiving stilbestrol and testosterone obtained the same relief from menopausal symptoms but in addition there was a higher incidence of a sense of well-being and increased libido. Also there was a significant decrease in the amount of nausea, breast turgidity, and pelvic congestion. Mild acne, hoarsness, or increase in facial hair growth was produced by this therapy in 13.2 per cent of the cases, but these masculinizing effects regressed soon after the therapy was discontinued.

In both of the preceding courses of therapy the improvement in the hypoestrogenic vaginal smear was a constant finding.

The courses of therapy with testosterone alone were interesting, in that no vaginal cytological changes appeared when it was the initial therapy and proportionately few patients experienced relief of symptoms. However, when used subsequently to estrogen or estrogen and testosterone treatment the improvement in symptomatology and vaginal cytology was apparently perpetuated.

The response to placebo therapy was, as was to be expected, disappointing.

It was concluded that the combination of estrogen and androgen gave, all factors considered, the best results.

C. J. EHRENBERG

Greenblatt, Robert B., and Barfield, William E.: The Effect of Intravenous Estrogen in Uterine Bleeding, J. Clin. Endocrinol. **11**: 821, 1951.

One of the authors (Greenblatt) previously has described functional uterine bleeding as bleeding which occurs because of physiologic disturbances and not because of pathologic processes. Consequently, in the present study organic and systemic causes of uterine bleeding were ruled out, such as malignant neoplasms, cervical polyps, pregnancy states, blood dyscrasias, infection, and metabolic disturbances such as hypothyroidism. Hormonal dysfunction is considered the chief cause of functional uterine bleeding, although nutritional, vitamin, nervous, and psychological factors may be contributory. Pelvic inflammatory disease, endometriosis, endometrial polyps, and uterine myomas may be included in the category of functional bleeding because the response to therapy is similar to that of excessive uterine bleeding which is purely functional and it is postulated that the mechanism of bleeding may be the same.

Menstruation is believed to be the result of hormonal (estrogen and progesterone) withdrawal after the proper sequence conditioning of the endometrium, although ovarian dysfunction, which may be primary or secondary to abnormal pituitary or hypothalamic states resulting in unruptured follicle, may produce endometrial bleeding after withdrawal of prolonged estrogenic stimulation.

It is pointed out that abnormal uterine bleeding or amenorrhea may occur in the face of proliferative, hyperplastic, progestational, acyclic, or atrophic endometria. Hemostatic control while satisfactory with estrogen, progesterone, and testosterone, alone or

in combination, frequently results in subsequent undesirable withdrawal bleeding. The present study is an evaluation of the use of a newer potent estrogen used intravenously.

Sixty episodes of uterine bleeding in 56 patients ranging from 15 to 56 years of age were treated by the intravenous injection of 5 c.c. of an aqueous solution containing 20 mg. of conjugated natural estrogens (equine) (Premarin). Medical history was obtained and preliminary physical examinations were performed on each patient. Capillary fragility tests and complete blood counts were made routinely. Vaginal smears, endometrial biopsies, and almost daily pelvic examinations were made after control of the bleeding. Early in the study the injections were repeated from one to three times daily. Later the interval between injections was reduced to from 6 to 12 hours for 2 to 4 doses or until the cessation of bleeding. To prevent withdrawal bleeding oral Premarin, 1.25 mg., was given 4 times daily for 5 days and then withdrawn gradually by reducing the dosage by 1 tablet every 5 days. In patients approaching the menopause Premarin, 0.625 mg., was continued for another week. However, in the younger patients progesterone therapy was used to induce bleeding and endometrial shedding, either Progesterone by ingestion, 30 mg. three times a day, anhydrohydroxy progesterone by ingestion, 10 mg. three times a day, or buccal progsterone, 10 mg. three times a day for 5 days.

In the 60 courses of treatment in the 56 patients, one case of adenocarcinoma of the uterine body and two cases of ectopic pregnancy were discovered subsequent to the origin of the treatment. In the remaining 57 courses of treatment, 48 produced satisfactory responses, 5 resulted in temporary amelioration, and 4 were failures. The 4 failures occurred early in the study, 3 patients having received only 1 dose of intravenous estrogen therapy and the fourth received a second dose 24 hours after the first injection. The 3 failures subsequently responded to estrogen, progesterone, testosterone therapy and the fourth failure proved to be a case of subinvolution of the uterus following spontaneous abortion.

Although the usual pathology as revealed by endometrial biopsy was cystic glandular hyperplasia or imperfect secretory endometrial development, fibromyoma, pelvic inflammatory disease, and neurofibromatosis were also discovered.

It is concluded that estrogens prepared for intravenous administration may be successfully employed in the arrest of functional uterine bleeding.

C. J. EHRENBERG

Astwood, E. B.: The Use of Antithyroid Drugs During Pregnancy, J. Clin. Endocrinol. **11:** 1045, 1951.

Recent studies indicate that the incidence of pregnancy with concurrent hyperthyroidism is what might be expected of the chance coexistence of the two conditions. Literature over the past thirty years indicates that the incidence of abortion and stillbirth although lessened by the treatment of hyperthyroidism during pregnancy with Lugol's solution, with or without subtotal thyroidectomy, remains considerably higher than in the normal pregnant woman. Hypothyroidism produced by overtreatment may lead to fetal loss in early pregnancy and myxedema in later pregnancy which, while not incompatible with normal pregnancy termination, may result in compensatory enlargement of the fetal thyroid.

The use of radioactive iodine during pregnancy seems contraindicated because Chapman, Corner, and Robinson found that after the third month significant amounts of the substance collected in the fetal thyroid.

Nineteen patients who became pregnant during or shortly after antithyroid therapy for hyperthyroidism were observed over the course of six years. Patients were seen every 4 to 6 weeks for dosage adjustment. Usually 100 mg. of propylthiouracil every eight hours were used until the patient became euthyroid when the dosage was reduced to 50 mg. Mercaptoimidazole was also employed in dosages alone of either 100 mg. daily, or 5 mg. every eight hours, or following the administration of propylthiouracil. No iodine was used, hyperthyroidism was controlled, there were no hypothyroidism or side effects and thyroid was prescribed in only one instance.

Twenty-five instances of pregnancy were recorded in this series of cases with 3 not completed. Twenty-two children were born alive and lived, none with goiter, thyroid disturbance, or malformation. Pregnancy terminated prematurely in 3 instances.

The thyrotoxicosis in no instance began during pregnancy. In 12 cases it occurred while the patient was not pregnant and in 7 instances it followed termination of pregnancy either full term or abortion.

Ten of the 19 patients before treatment manifested signs of impaired fertility such as menstrual irregularity, failure to conceive, abortion, or death of the newborn with malformation.

This study corroborates the view of Mussey and Javert that pregnancy influences thyrotoxicosis not at all and in some instances is ameliorative. Antithyroid drugs not only easily controlled the disease in pregnancy, but resulted also in a high incidence of lasting remissions. In 18 patients who had completed one course of treatment and had undergone at least one pregnancy, 15 remained in good health after treatment was discontinued, the remissions lasting from 2 years to 5 years in 13 cases.

It is concluded that pregnancy is beneficial to hyperthyroidism and that antithyroid therapy alone is an effective form of treatment.

C. J. EHRENBERG

Gynecology

Arenas, Normando, and Bottaro, Hugo C.: New Contribution to the Treatment of Pelvic Inflammatory Processes in the Female by Local Injection of Penicillin-Novocain. An. Clin. Ginec. y cir abd. del; Hospital Ramon, Mejia, Buenos Aires 2: 62 and 198, 1948-1949.

The authors report their personal experience with 35 patients having acute pelvic inflammatory disease, in whom 262 intrapelvic injections of penicillin-Novocain were made through the vaginal fornices in 101 sittings. An additional 23 cases are reported subsequently (page 198), makng a total of 58 cases and over 500 injections.

The solution used consisted of 1 per cent Novocain with 5,000 to 20,000 units of penicillin per cubic centimeter. An ordinary syringe with a needle 12 to 15 cm. long was used.

After locating the site of the inflammatory process by pelvic bimanual examination, a vaginal speculum was inserted, the posterior cervical lip grasped with a suitable toothed instrument, and the desired fornix exposed. The needle was then inserted and pushed up to the lesion; aspiration was carried out and any collected fluid or pus evacuated, after which the Novocain-penicillin solution was injected through the same needle. The procedure was repeated in other fornices if indicated. Posterior colpotomy was performed when an abscess was present in the cul-de-sac of Douglas.

Pain was relieved immediately after the injection, although in a few cases the patients experienced transient sharp abdominal pains.

In suppurative cases the injection is sometimes followed by a transient elevation of temperature of one or two degrees, after which a fall in temperature and subjective and objective improvement occur. Injections are repeated from one to six times at 24- to 62-hour intervals.

According to the authors, there are no contraindications by reason of menstruation, menorrhagia, age, severity of infection, or general diseases (diabetes, etc.).

Intramuscular penicillin was used concurrently in cases where the involvement was extensive or had spread beyond the pelvic organs.

The authors are convinced of the effectiveness of this treatment in rapidly resolving acute inflammatory processes of the pelvis. No complications due to the procedure were encountered.

MAGIN SAGARRA

Gallegos, A. Dominguez: Treatment of Intestinal Fistulae by Implantation of Placenta, Rev. obst. y ginec., Caracas **11**: 200, 1951.

The author reports 4 cases of postoperative intestinal fistulas treated by implantation of fresh placenta. The technique used consisted of: (1) exposure of the margins of the fistulous opening under local anestheesia; (2) packing of the entire fistulous tract with strips taken from fresh placental cotyledons, the greatest possible amount being introduced. Fresh placenta immediately after its delivery was used in 3 cases, and within four hours of delivery in one (the placenta being kept in normal saline with penicillin in the interim); (3) approximation of the margins of the fistulous opening over the implant whenever possible, followed by pressure dressing.

Evolution of implant: The pressure dressing was removed in 72 hours, and the placental tissue found to have undergone decomposition and elimination, as well as the sutures when employed. However, on subsequent days the walls and margins of the fistula began to granulate and the fistula was completely healed in an average of 15 days. The placental tissue does not behave as a transplant; it undergoes necrosis and elimination, but apparently acts by activating granulation and secondary union.

Seventy-five per cent success was obtained by this method, 3 cases being cured with 1 failure.

MAGIN SAGARRA

Labor, Management, Complications

Chalmers, J. A.: Premature Separation of the Normally Situated Placenta Due to Foetal Suicide, J. Obst. & Gynaec. Brit. Emp. **58**: 33, 1951.

Many cases of premature separation of the normally situated placenta are associated with pre-eclamptic toxemia. Others are caused by various nontoxic conditions and a very small number of these can be attributed to short cord, relative or actual. The author applies the term "foetal suicide" to those cases where traction on the shortened cord detaches the placenta. The umbilical cord may actually be so short that as descent of the presenting part takes place traction finally detaches the placenta; or due to coils about the body or extremities or both the cord becomes sufficiently taut to cause detachment of the placenta and fetal death. A case illustrating the latter accident is given in detail.

Your reviewer must take issue with the author in his use of the phrase "fetal suicide." According to Webster "suicide is the act of self-destruction by a person of sound mind and capable of measuring his moral responsibility." Obviously "fetal death" is the more correct expression since the unborn fetus has no mind nor sense of moral responsibility.

HARVEY B. MATTHEWS

Gill, Robert C., and Farrar, James M.: Experiences with Di-hydro-ergotamine in the Treatment of Primary Uterine Inertia, J. Obst. & Gynaec. Brit. Emp. **58**: 79, 1951.

The causes of functional uterine inertia remain obscure; the treatment generally unsatisfactory. At best, management is always difficult and requires great patience and mature judgment. The distress of the patient and uneasiness of the family do not make the task any easier for the obstetrician. Many therapeutic agents have been used to combat uterine inertia; but none are universally successful. These drugs fall into two main groups, viz., antispasmodics and uterine stimulants. Examples of each group are discussed with comments regarding success or failure of several specific drugs, particularly the intravenous drip administration of Pitocin or Pituitrin. The authors have employed di-hydro-ergotamine, a synthetic derivative of ergot, in 43 cases of prolonged labor, 34 of which were considered successful. They discuss the pharmacology of the drug, its clinical response, the safety of mother and child, and offer suggestions as to indications,

dosage, and method of administration. Their recommended dose is 0.25 mg. given intramuscularly. Larger doses, they feel, are unnecessary and they may produce excessive uterine activity. The injection may be repeated two or three times at 4-hour or longer intervals but usually two doses are sufficient.

HARVEY B. MATTHEWS

Malignancies

Meigs, Joe Vincent: Removal of the Pelvic Lymph Nodes in Cancer of the Cervix. The Transperitoneal (Taussig) and Retroperitoneal (Nathanson) Dissection, Gynéc. pratique 2: 115, 1951.

Meigs, as an honored guest lecturer before the International Cancer Congress held in Paris in July, 1950, reviews his experiences in gynecic surgery concerned with carcinoma of the cervix uteri.

Meigs reiterates that by the use of selected lymphadenectomy operations there can ensue a greater salvage of carcinoma of the cervix cases whose local lesions exhibit post-radiation control. Again the author emphasizes that these operative methods of treatment are indicated in selected cases particularly because it is felt that x-ray treatment as given at the present time cannot destroy cancer in the pelvic lymph nodes. He quotes Morton's, Taussig's, and Nathanson's lymph node findings in support of this statement.

Meigs admits there exist serious operative dangers but concludes that, in his hands, the mortality and morbidity are minimal. He favors the retroperitoneal approach as possessing several advantages: (a) less risk, (b) wider applicability since it can be done in stages, and (c) better surgical exposure in the obese patients.

The writer concludes these operations are in the experimental stage but in the hands of the more qualified gynecologic surgeon they do represent an addition to our operative armamentarium. In his discussion Meigs does observe, "surgical dissection of a protected area may break barriers and allow dissemination of the tumor to occur. This phenomenon has been noted in our series and it makes one wonder whether or not surgery by destroying barriers may allow dormant and imprisoned carcinoma to reactivate and spread."

CLAIR E. FOLSOME

Thorp, Donald: Ovarian Carcinoma Subsequent to Hysterectomy, West. J. Surg. **59**: 440, 1951.

A plea is made for the removal of the ovaries at the time of hysterectomy. An enthusiastic and brilliant espousal of this surgical philosophy is underscored by the report of ten malignant neoplasms arising in the ovary left in place after hysterectomy. In a period of five years there were two hundred seventy-six pelvic tumors removed from women upon whom hysterectomy had previously been performed and in whom one or both ovaries had been left. Ten of these tumors were malignant neoplasms which at the time of this report had brought death to five of the patients.

The author feels that the best interest of the patient is not served by leaving the ovary following this operation. He believes that the symptoms of the climacteric following bilatral oophorectomy are no more severe than those following physiological ovarian involution. The ovaries are unpredictable organs and even those which do not undergo malignant change after hysterectomy are all too frequently the site of cystic degeneration which vitiates their possible physiologic usefulness. The author muses on the thousands of appendices which have been removed prophylactically when the worst fate of that organ is inflammation and not malignancy while traditional reverence for the ovaries precludes their removal at a time when their useful function is nullified by removal of the uterus.

WILLIAM BICKERS

Roman, C., Vincent, E., and Feroldi, J.: Primary Chorionephithelioma of the Ovary, Gynéc. et obst. 48: 512, 1949.

The authors describe, with considerably well-documented detail and photomicrographs, a case of primary chorionepithelioma of the ovary in a nulliparous woman 25 years of age.

CLAIR E. FOLSOME

Miscellaneous

Alvarez-Zamora, Ramiro: Contribution to the Study of Rhabdomyoblastoma, Grape-like Sarcoma of the Vagina in Children, Doctoral Thesis from the Spanish Collection, Published by the Library of Medical Sciences, Barcelona, 1950.

In an 82-page monograph the author describes 3 new cases of grapelike sarcoma of the vagina of children. He reviews the world literature upon this rare neoplastic disease, reporting his summary from data available upon 72 such cases in his total series.

These "grapelike" sarcomas of the vagina in children are characterized by their "grapelike" appearance. They are soft, translucent, pale in color, though at times red to bluish because of hemorrhagic extravasations. These tumors occur most frequently in the first two years of life and their most common point of origin is on the anterior vaginal wall. Their growth is by contiguity primarily toward the introitus. In the advanced stages they infiltrate, by direct extension, and metastases are rare. Simple extirpation, however, inevitably leads to a fatal outcome with frequent recurrences.

Bladder symptomatology appears early because of urethral or vesical neck compression. Later symptomatology becomes more serious because of subsequent ureteral dilatation, bladder distention, cystitis, and hydronephrosis.

The author utilizes a silver impregnation stain to study these tumors. From such study he affixes the term rhabdomyoblastoma because of their cross-striated, muscular, embryonal characteristic microscopic pictures. These tumors contain no elastic or smooth-muscle fibers, only fine fibrils of reticulin and precollagen. He remarks that other authors often use the descriptive terms "fibrosarcoma," myxosarcoma, round- or spindle-cell sarcomas. In his opinion the employment of a more adequate silver stain would rule out such pathological connotations.

The author discusses three theories explanatory of their origin, Colinheim's, Wilm's, and Meyer's theories. In his opinion all theories explain in part their derivation from the excretory ductile anlage of the Wolffian mesonephros.

Prognosis in these tumors is extremely poor. Among the known 72 cases, only 3 patients survived following 15 years of observation. Surgery is contraindicated and the greatest though scant hope for arrest is obtained with use of radium and x-ray therapy. Thirteen photographic figures and a large summary sheet, from 1854 to 1945, are included in this excellent monograph.

CLAIR E. FOLSOME

Lévy-Solal, E., Valette, Mme., Lanvin, M., and Perex, M.: Observations on Blood Levels of Chloroform in the Maternal and Fetal Blood Where Chloroform Was Employed During Forceps Application, Bull. Féd. Soc. de gynéc. et d'obst. de langue franç. 3: 371, 1951.

The authors, working at Bandelocque Clinic, decided to review chloroform as an obstetrical anesthetic for two reasons: (a) it is still used as an obstetrical anesthesia in many French Maternity Hospitals, and (b) they now have methods to evaluate its concentration in the blood of the mother and infant after short employment during forceps application.

The chloroform was administered by a closed system, using the Ricard apparatus, with exact quantities known at the outset. They kept exact record of the time of the

anesthesia, clinical condition of mother and infant, and took immediate adequate venous maternal and infant cord blood specimens. Their method of calculating chloroform in the blood specimens is given in detail.

In 7 cases the chloroform values of the fetal blood were higher, averaging 139.25 mg. for fetal blood and 73.0 mg. for maternal blood. In 3 additional cases, not following this general finding, the values were 122.0 mg. in maternal venous blood and 82.0 mg. in fetal cord blood. In 4 cases where blood chloroform levels were taken after oxygen therapy it was observed that the values of the cord blood specimens were greater than those from maternal venous blood. The writers conclude that oxygen therapy after short use of chloroform in obstetrics decreases the chloroform blood level in the fetal cord blood. In the cases cited chloroform was used approximately ten minutes on the average, and approximately 10 Gm. were used during the average obstetrical episode.

CLAIR E. FOLSOME

Butler, E. Blanche: A Case of Hypersensitivity to Pethidine in a Woman in Labour, Brit. M. J. **2**: 715, 1951.

A patient was given 100 mg. intramuscularly of pethidine (Demerol) 4 hours after the onset of labor at which time the cervix was 3 cm. dilated. Some 3 hours later, when the fetal heart tones were of good quality, she suddenly became cyanosed, developed a rash, the pulse became imperceptible, and the blood pressure could not be obtained. Five minuts after the onset of these signs a stillborn infant was delivered. Recovery took about 2 hours. Later 50 mg. of pethidine were injected intramuscularly as a test and 4 hours later the systolic blood pressure dropped 20 mm. Hg.

It was concluded from this test that the reaction during labor was attributable to the administration of pethidine.

R. GORDON DOUGLAS

Romani, M. J. D.: The Prevention of Lactation by Estrogens. The Prevention of Lactation by Orally Administered Dienestrol, Gynéc. et obst. **49**: 312, 1950.

The author reports upon his experience in the use of dienestrol, given orally, for the purpose of halting lactation in 24 cases. He found that dienestrol was seven and one-half times more active than diethylstilbestrol and that the optimal dosage was 3.0 mg. daily for 5 days beginning 24 hours after delivery.

CLAIR E. FOLSOME

Placenta

Danesino, V., and Wiedermann, K.: The Microscopic Study of the Ramifications and Characteristics of the Fetal Vessels in the Human Placenta, Arch. ostet. e ginec. **55**: 471, 1950.

Much work has been done on the spiral arteries of the endometrium, the ovary, and umbilical cord, but descriptions of the placental circulation have been infrequent and sketchy. The authors became interested in the placental vessels with their characteristic ramifications and structure.

In order to effect a three-dimensional study, casts were obtained of the placental vascular tree, using a celluloid medium for injection followed by corrosion with hydrochloric acid. Forty fresh placentas from the fourth to the ninth month of gestation were used. These were carefully measured and weighed, and form and insertion of the cord noted.

The authors indicate that the factors which influence the development of the placenta also affect the disposition of its vessels. The vascular tree of the placenta is greatly influenced in its structure as well as in the number and size of its branches by the degree of maturity of that organ and its topographical position. The volume of the pla-

centa is in inverse proportion to the size of the uterus. The number of precapillary and capillary vessels is directly proportional to the volume of the placenta, whereas its main branches are not so affected, except that at term these vessels assume a rectilinear pattern. At the insertion of the cord, the main vessels describe a semicircular course without sending out any collateral vessels before terminating in the cotyledons. The authors feel that there is a physiological reduction of cotyledonary flow approaching term (as demonstrated by casts of the placental tree). It is a fact that the 7-month fetus has approached relative maturity and that from the seventh to the ninth month growth and development predominate and the maternal blood flow may decrease proportionately, for the new being is beginning to assume complete autonomy. The authors discuss in detail the ramification of placental circulation, describing the arteries and veins of the placenta, the pattern they form as they branch in the cotyledons terminating in the villus tree. There are numerous fine photographs of the vascular casts obtained in the various stages of gestation.

LOUIS J. SALERNO

Pregnancy, Complications

Haeger, K.: A Review of Pelvic Tumors Arising Extragenitally and Obstructing Delivery, Acta obst. et gynec. Scandinav. 30: 391, 1951.

The author reports the case of a 24-year-old woman, pregnant at term, in whom rectal examination during a nonprogressing labor brought to light a hard tumor mass intimately related to the right pelvic wall, and apparently impeding descent of the fetal head. Uneventful cesarean section was performed, and two months later the patient was surgically explored. The tumor, which was thought not to be of osseous origin from preoperative x-ray studies, was found to be firmly attached to the lower part of the pubic and ischial bones; it was easily removed, and proved to be a fibroma. Postoperative recovery was uneventful.

One hundred cases of tumors obstructing delivery were collected from the literature. Most of these were tumors derived from bony or cartilaginous tissue (68 cases); fibroma-like tumors were found in 23 cases. Ten tumors of bone and cartilage were classified as malignant neoplasms: seven as osteogenic sarcomas, and one each as myxosarcoma, spindle-cell sarcoma, and chondrosarcoma. The most frequent site of origin of these bony tumors was the anterior surface of the sacrum, particularly the upper three vertebrae; the sacroiliac synchondroses were also frequently noted as starting points. These tumors characteristically reach very large size without producing untoward symptoms. Parity does not seem to be a significant factor in influencing their incidence. The majority of the patients in whom these tumors were diagnosed during labor were delivered by cesarean section. Extirpation of the tumor is usually done at a later date.

DOUGLAS M. HAYNES

Hølund, T.: Spontaneous Rupture of the Uterus During Pregnancy, Acta obst. et gynec. Scandinav. 30: 408, 1951.

On the basis of 92 cases of rupture of the uterus during pregnancy, the author analyzes the recorded symptomatology in an effort to arrive at definitive diagnostic criteria. Abdominal pain was reported in all 92 cases, and it was usually violent and of sudden onset. In 10 cases, the pain ceased completely on the day of onset. Actual collapse was reported 15 times and syncope 18 times; so absence of these symptoms in the initial stage of the disease does not exclude uterine rupture. Collapse occurs with complete rupture with expulsion of the fetus into the abdominal cavity. Vomiting occurred in 26 cases, and was apparently due to incipient or manifest peritonitis. Cessation of fetal movements was noticed in 10 cases as one of the earliest signs. Vaginal bleeding was observed 12 times. Objective signs depend on the rapidity with which rupture occurs, on its site, and on how soon after rupture the patient is examined. In the cases collected here, the

fetus could be palpated lying free in the abdomen 10 times. More often, however, the uterus is relatively normal to palpation, though tenderness and tenseness are present. A mistaken diagnosis of abruptio placentae tends to be made for this reason. Signs of peritoneal irritation were reported in 25 per cent of the cases. Abdomen and uterus were entirely normal to palpation in 5 cases. Temperature was elevated only when there was concomitant peritonitis. Gradually developing anemia in patients under observation served as an indication for operation in 30 of the patients. The author emphasizes that the presumptive diagnosis of uterine rupture should be made before the slowly developing anemia has become severe. Review of these cases corroborates the conclusions of numerous authors that rupture of the uterus should be suspected in cases of acute abdominal pain of sudden onset during the latter half of pregnancy, especially after the eighth month. By making use of careful evaluation of physical signs—fetus free in abdominal cavity, tender or tense uterus, absence of fetal heart sounds, anemia, and signs of peritoneal irritation—timely exploratory laparotomy may be performed and the mortality of this obstetric catastrophe may be reduced.

DOUGLAS M. HAYNES

Krieger, Vera I., and Butler, Hildred M.: Antidiuretic Substance in the Urine During Pregnancy and Its Frequent Association With Bacterial Growth, J. Obst. & Gynaec. Brit. Emp. **58**: 5, 1951.

The authors found that when the specimens of urine were collected over a standard period of time and reduced to a constant volume, a more reliable index of the amount of antidiuretic substance excreted could be obtained. Estimates were made from urine from men, and from nonpregnant, normally pregnant, and toxemic pregnant women, all of which showed the presence of an antidiuretic substance. These findings refute the original contention that the presence of an antidiuretic substance in the urine was characteristic of toxemic pregnancy. Due to the severe toxicity of these urine concentrates to mice, often causing death, it was suggested that this toxicity might be due to infection by *B. coli* and therefore it could not be accepted as evidence of the excretion of antidiuretic pituitary substance. This hypothesis was tested out and the conclusion reached that contamination with bacteria, particularly *B. coli,* markedly vitiated the results, and unless complete sterility could be maintained throughout the experiment no definite conclusion could be reached. In view of this finding it is doubtful that an antidiuretic substance of pituitary origin can routinely be detected in sterile urine from toxemic patients.

HARVEY B. MATTHEWS

Sauramo, H.: Hypotensive Obstetric Patients With Special Reference to Gestosis, Acta obst. et gynec. Scandinav. **30**: 351, 1951.

The patients discussed in this paper were women being followed in the outpatient clinic of the First Women's Clinic, University of Helsinki. Patients who had a systolic blood-pressure reading of 110 mm. of mercury at any time during pregnancy were included in the study provided that the hypotension was not the expression of an obvious acquired illness such as severe anemia, cardiac insufficiency, long-standing debilitating disease, carcinoma, or posthemorrhagic syndrome. The average incidence of hypotension in pregnant women for the period 1935 to 1948 was 7.2 per cent, with a diminution in incidence during the war years, possibly attributable to continuous strong psychogenic stress. Subjective symptoms probably related to the hypotension were observed in 20 per cent of the hypotensive gravidas. These symptoms include weakness, fatigability, vomiting, palpitation, precordial oppression, indigestion, epigastric distress, and headache. Hypotensive gravidas tend toward an asthenic body build. They were generally found in this series to be less than 40 years of age. The total frequency of toxemia in this group was 9.2 per cent, and the grade of toxemia was, in general, mild. Patients with a consti-

tutional tendency toward hypotension would appear to be excellent candidates for pregnancy and delivery; when toxemia is superimposed, it tends to be mild, and associated symptomatology is not obstetrically deleterious.

DOUGLAS M. HAYNES

Swanberg, H., and Wiqvist, N.: Rupture of the Umbilical Cord During Pregnancy, Acta obst. et gynec. Scandinav. **30**: 323, 1951.

The authors review the literature on rupture of the umbilical cord, and compile a table of etiological factors concerned. To two reported cases of rupture of the umbilical cord during pregnancy they add a third. Etiological factors are divided into traumatic injuries, anatomical abnormalities, degenerative changes, inflammatory lesions of blood-vessel walls, and toxic lesions of blood-vessel walls. Traumatic injuries may be due to stress arising from the forces of expulsion; to mechanical compression; to pressure changes during delivery; to sudden escape of large quantities of amniotic fluid; or to injury from operative delivery. Anatomical abnormalities include absolute or relative shortness of the cord, velamentous insertion, and varices or torsions. Among the degenerative changes which may predispose to rupture are unusual looseness of structure of Wharton's jelly and connective tissue; deficiency or absence of Wharton's jelly; deficiency or absence of the tunica elastica of blood vessels; attenuation of blood-vessel musculature; mucoid degeneration; and hereditary or constitutional weaknesses. The principal inflammatory disease which may be operative is syphilitic involvement of the walls of the cord vessels. In the case reported by the authors, the most striking feature was an abnormal insertion of the cord in which the vessels separate before joining the placenta, insertio funiculi furcata. Fetal death in utero prior to the onset of labor occurred in this patient following a heavy fall on the buttocks; labor did not ensue until 12 days later. The possibility that the rupture may have followed motion of the fetal extremities is considered.

DOUGLAS M. HAYNES

Pregnancy, Physiology

Kulseng-Hanssen, K.: Maintenance of Early Pregnancy Despite Extirpation of Three Corpora Lutea, Acta obst. et gynec. Scandinav. **30**: 420, 1951.

The clinical protocol of a 39-year-old parous woman who was subjected to exploratory laparotomy because of vague pain in the hypogastric region and back is presented. No amenorrhea or other symptoms or signs of pregnancy were complained of, so when at operation three distinct corpus luteum cysts were encountered, these were thought to be her primary "disease," and were removed. Three weeks after operation, the patient experienced vomiting and constipation, and was readmitted; at this time, an early pregnancy episode was diagnosed. The vomiting was controlled, but five weeks later the patient became the victim of a serious mental depression, and hysterotomy and sterilization were done on psychiatric recommendation. A viable twin-ovum pregnancy corresponding in size to a conceptus of three months' gestation was found at operation.

The case history illustrates undisturbed continuation of early pregnancy after extirpation of corpora lutea in about the fourth week of pregnancy. The author assumes that even at this early stage the chorion produces sufficient progesterone for the maintenance of pregnancy. The pertinent literature is reviewed.

DOUGLAS M. HAYNES

Anzisi, G., and Vaglio, N.: Serum Concentration and Urinary Excretion of Chorionic Gonadotropins in Pregnancy, Arch. ostet. e ginec. **55**: 496, 1950.

The scope of this paper is to determine the variation in the levels of chorionic gonadotropin in the blood serum and urine of pregnant women in the third trimester who manifest varying degrees of toxemia of pregnancy. The authors employed the male *Rana*

esculenta, considering one R.U. (Rana unit) to be that smallest amount of serum or urine which, injected intraperitoneally, provokes emission of sperm in three to six hours. This is the equivalent of eight international units.

Selecting 50 subjects, the authors made 700 determinations of serum and urinary chorionic gonadotropins. The patients were divided into three groups with the following results:

Group I. Patients with edema and/or albuminuria but without hypertension.
15,000-16,000 I.U. chorionic gonadotropin in blood serum
6,000-8,000 I.U. chorionic gonadotropin in urine

Group II. Patients with edema, albumin, and hypertension, and general symptomatology of pre-eclampsia
90,000 I.U. chorionic gonadotropin in serum
240,000 I.U. chorionic gonadotropin in urine

Group III. Patients with eclampsia
14,000 I.U. in serum
180,000 I.U. in urine

Urinary excretion of the hormone may give indication of its metabolism representing perhaps the quantity of gonadotropin not utilized or destroyed in the organism itself. Serum gonadotropin and its urinary excretion vary in many conditions complicating pregnancy, especially in pre-eclampsia. There appears to be a definite reversal of the serum gonadotropin/urinary excretion ratio in toxemic conditions where there is an alteration of the normal equilibrium of pregnancy. This ratio of serum gonadotropin to urinary excretion levels may have useful diagnostic import, indicating perhaps the turning point from incipient toxemia of pregnancy to full-blown pre-eclampsia and eclampsia.

LOUIS J. SALERNO

Toxemia

Bergqvist, N.: Potassium Deficiency in Hyperemesis Gravidarum, Acta obst. et gynec. Scandinav. **30:** 428, 1951.

Detailed clinical data are reported concerning the case of a 25-year-old woman, 5 months pregnant, who had been troubled with relatively severe vomiting for three months, with a marked exacerbation for 3 weeks prior to admission. There was no icterus, fever, or albuminuria; a moderate tachycardia was present. There was sudden onset of hypotension, mental confusion, and muscle weakness, associated with considerable drop in serum chloride, potassium, and calcium levels. Death occurred in 36 hours. The relationship of this fatal syndrome to the demonstrated hypokalemia is discussed. The clinical evidences of potassium deficit include skeletal muscle hypotonia and electrocardiographic changes (depression of T-waves and S-T segment below the isoelectric line), both of which were observed in this patient. Because of a postulated disturbance in the selective permeability of cell membranes with consequent passage of potassium from the cells, the serum potassium level may be normal or even increased despite intracellular potassium deficiency; for this reason, the electrocardiographic evidences of hypokalemia are of considerable practical importance. Not only did the potassium level fall in the patient described, but at the time of her acute collapse there was concomitant fall in chlorides, calcium, serum proteins, sodium, and bicarbonate; peripheral circulatory collapse under these conditions is assumed to be due to inability of the cell membrane to maintain its relative impermeability for sodium because of deficiency in intracellular electrolytes. Invasion of the cells by sodium ions, and probably also by chloride ions, then ensues, with associated acute intracellular edema with sudden fatal issue. Signs suggestive of polyneuritis—hypoactive reflexes, paresis of the extremities—were observed in the patient

reported in spite of administration of large amounts of vitamin B; it is suggested that polyneuritis-like syndromes complicating severe hyperemesis gravidarum should be investigated from the standpoint of possible hypokalemic myoplegia.

DOUGLAS M. HAYNES

Garrett, Sherman S.: Minerals in the Etiology and Treatment of Eclamptic Toxemia, West. J. Surg. 59: 366, 1951.

In order to understand the role of minerals in eclamptic toxemia certain physiological concepts must be borne in mind. Minerals are ionized and any attempt to interpret the action of body minerals in eclampsia in terms of their salts is fruitless. Because of the difficulties entailed in sodium and potassium determination a relatively simple test for chlorides is often substituted. Attempts are then made to interpret these findings as though they actually represent a measure of sodium and such conclusions as are drawn from the chloride studies must inevitably lead to error.

The intracellular fluid, the intercellular fluid, and the blood serum or plasma are relatively stable media in health but their equilibrium is disturbed in disease. Blood is so readily available for testing that it is common practice to take samples of it and deduce from examination of the blood that which is occurring in other body fluids. This practice leads to erroneous reasoning.

The most important cause for the morbidity and mortality of eclampsia is a disturbance of intracellular physiology characterized by loss of potassium and an increased amount of sodium and other intracellular changes which the author feels are induced by certain activity of the adrenal steroid hormones. The renal and hepatic lesions of eclampsia are largely a result of the disease process rather than the cause. Excessive intake of salts is harmful to the toxemic patient because sodium ion aggravates the intracellular mineral imbalance. Potassium, calcium, ammonium, and the chloride and sulfate ions are beneficial in the treatment of eclampsia because they tend to restore to normal the intracellular mineral imbalance characteristic of this disease. In like manner glucose favors a re-establishment of normal electrolyte equilibrium in the intracellular fluid. The electrolyte changes which occur in eclampsia are those which one would expect from excessive activity of the adrenal steroid hormones. The sodium retention, the abnormally increased elimination of potassium favor the storage of water and the clinical signs of the disease. It is also said that a chloride deficiency induces some of the same changes as those resulting from potassium deficit. Calcium has a capacity to prevent intracellular shift of potassium. Phosphorus is probably involved in the altered metabolism in eclampsia because intracellular fluid is rich in phosphorus which is an essential part of the glucose utilization mechanism.

The author concludes that practically all of the clinical findings in eclampsia and severe pre-eclampsia can be traced to the distuurbed mineral metabolism resulting from excessive activity of the adrenal steroids. It is hypothecated that these adrenal steroids may be the long-sought "toxin" in the toxemias of pregnancy. Prevention of eclampsia then should consider the electrolyte changes which favor the disease. A high potassium intake promotes elimination of sodium and likewise the ammonium salt of the chloride as well as calcium tends to counteract the changes favoring the development of toxemia. Likewise, glucose during its conversion into glycogen causes potassium to enter the body cells and promotes the excretion of sodium. Those ions which favor such an exchange are clinically useful in the prevention and treatment of the toxemias of pregnancy.

WILLIAM BICKERS